study of repeated administrations of dosages of 16 mg i.v., at half-hour intervals, was made to explore the possible development of short-term tolerance and none was observed.

In the definition of DMT either as an endogenous psychotogen or, equally appealing, as a natural neurotransmitter, it would be desirable to show that the body does not build up long-term tolerance to it (otherwise the psychotic would spontaneously repair, and the brain would spontaneously shut down). To address this, four subjects were given some 50 mg of DMT intramuscularly, twice daily, for 5 days. The blood levels that were achieved, and the picture of autonomic effects (both in mydriasis and in cardiovascular function) were not changed. No tolerance was seen. The psychological conclusions were a little bit less convincing. Several subjects said that the "high" was diminished, but others seemed to feel a maintenance of subjective responses. The jury is still out on this one.

Thanks to the developement of ever-increasingly sensitive scientific instruments, the search of body fluids for possible psychedelics has brought forth a number that appear to be natural components of the human animal. DMT has been reported to be in the urine of schizophrenic patients, and so have 5-MeO-DMT, bufotenine, and its demethylated homologue N-methylserotonin. The levels are increased with the administration of monoamineoxidase inhibitors. A methylating enzyme has been found in blood, capable of forming DMT in plasma, and it is present in both normal subjects and schizophrenics. It is not surprising that studies comparing DMT blood levels between patients (psychotic depression, acute and chronic schizophrenia) and normal subjects have shown no differences. The ubiquitous nature of DMT touches upon a couple of delicate points. It was first a man-made compound, synthesized in Canada in the early thirties. Then some twenty years later it was discovered in the plant world as a natural product. This puts a delicate weapon in the hands of the "natural is better than synthetic" argument often voiced. Then, as mentioned here, it has proven to be a natural, normal component of human metabolism, making the wording of Federal Drug law interesting, as the section in the Schedule I hallucinogens implies (in a phrase that lacks a verb and hence a specific meaning) that the possession of any quantity of any form of any listed substance (such as DMT) is illegal. Our brains are illegal?

The principal reason that DMT must be administered parenterally is its rapid and efficient metabolism. It can be oxidized to the N-oxide. It can be cyclized to β-carbolines, both with and without an N-methyl group. It can be N-dealkylated to form NMT and simple tryptamine itself. Best known is its oxidative destruction, by the monoamine oxidase system, to the inactive indoleacetic acid. There is a wild biochemical conversion process known for tryptophan that involves an enzymatic conversion to kynurenine by the removal of the indole-2-carbon. A similar product, N,N-dimethylkynurenine or DMK, has been seen with DMT, when it was added to whole human blood in vitro.

Several simple substitution derivatives of DMT are known. Those that are known to be psychedelic have their own recipes, of course, but the others will be

summarized here. The 1-methyl homologue of DMT (1,N,N-trimethyltryptamine) can be prepared from DMT in KOH and DMSO, with CH_3I. It forms a picrate salt which melts at 175-179 °C, and bioxalate, mp 174-176 °C. It is more toxic than DMT in rats, but has an identical serotonin binding capacity. The compound with a methoxy group substituent at the 1-position is called Lespedamine, 1-MeO-DMT. With an NO bond, this should be classified as a substituted hydroxylamine. I would love to know if anyone anywhere has ever tried smoking it. I suspect it might very well be active, but it is, to my knowledge, untried. I wonder why it deserves a trivial name, vis., Lespedamine? Two additional ring-substituted derivatives of DMT come from the marine world. 5-Bromo-DMT and 5,6-dibromo-DMT are found in the sponges *Smenospongia auria* and *S. echina*, resp. I have no idea if they are active by smoking (the 5-Br-DMT just might be) but they are quantitatively reduced to DMT by stirring under hydrogen in methanol, in the presence of palladium on charcoal. A very closely related sponge, *Polyfibrospongia maynardii*, contains the very closely related 5,6-dibromotryptamine and the corresponding monomethyl NMT. I have the fantasy of trying to scotch the rumor I'm about to start, that all the hippies of the San Francisco Bay Area were heading to the Caribbean with packets of Zig-Zag papers, to hit the sponge trade with a psychedelic fervor. This is not true. I refuse to take credit for this myth.

The demethylated homologue mentioned above is N-methyltryptamine (NMT) and it is also widely distributed in nature. It has a synthesis in an entry of its own.

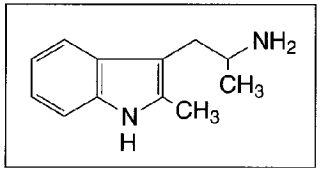
Both the N-hydroxy and the 2-hydroxy analogues of NMT are found in another legume, *Desmanthus illinoensis*, but have not been pharmacologically evaluated. Another provocative mono-alkyl analogue of DMT is N-cyclopropyltryptamine, made from indole-3-yl-glyoxyl chloride and benzyl cyclopropylamine with eventual hydrogenolysis of the benzyl group; mp 180-182 °C. This compound, as with the 5-methoxy and the 7-methoxy counterparts, is a potent monoamineoxidase inhibitor, and it has also been reported to have hypoglycemic activity. The 2-methyl-homologue of NMT was made from 2-methyl-3-(2-bromoethyl)tryptamine and methylamine. This is 2,Me-DMT (or 2,N,N-TMT). Both it and tryptamine itself (T) have their own entries.

Before this is closed, three points can be made regarding nomenclature. Older literature uses alpha for the 2-position of the indole ring. Thus, alpha-methyltryptamine, in early literature, refers to the indole-2-methyl, not to a side-chain methyl derivative. Throughout *TIHKAL*, the numbers are devoted to the indole ring, and the alpha and beta terms to the side-chain. And the use of the letter N refers to the side-chain amino nitrogen atom. The pyrrole nitrogen is the indole position 1. And finally, I found in my old files a news announcement (dated March 25, 1974) that Hercules Chemical Company intends to build a big DMT plant in the Southern United States, with an annual capacity of 800 million pounds a year. In the industrial world, DMT can also stand for dimethylterephthalate.

#7. 2,α-DMT; TRYPTAMINE, 2,α-DIMETHYL; INDOLE, 2-METHYL-3-(2-AMINO)PROPANE; 2-α-DIMETHYLTRYPTAMINE; 2-METHYL-3-(2-AMINO)PROPYLINDOLE; 2-Me-α-MT; ALPHA-2

SYNTHESIS: A solution of 4.78 g 2-methylindole-3-carboxaldehyde in 18 mL of nitroethane was treated with 0.77 g anhydrous ammonium acetate and heated on the steam bath for 2 h. The excess nitroethane was removed under vacuum and the residual orange-red solids were removed and washed with H_2O. After drying these were triturated under 25 mL MeOH, filtered and air-dried to constant weight. There was thus obtained 3.8 g (59%) of 1-(2-methylindol-3-yl)-2-nitropropene with a mp 146-148 °C.

To 250 mL of a room-temperature 1.0 M solution of LAH in THF, well-stirred and under N_2, there was added a saturated solution of 3.6 g 1-(2-methylindol-3-yl)-2-nitropropene in warm THF. The addition took place over 1.25 h, the reaction mixture was stirred for an additional 8 h, and then held at 40 °C for 8 more h. The slurry was then cooled in an ice bath and decomposed by the slow, sequential addition of 30 mL isopropyl acetate, 20 mL H_2O and, finally, 20 mL of 20% aqueous NaOH. The resulting alkaline suspension was extracted with 3x100 mL isopropyl acetate. The extracts were pooled, washed with 3x50 mL 10% aqueous NaOH, then extracted with 10% aqueous acetic acid. This extract was washed with isopropyl acetate, made basic with 20% aqueous NaOH, and extracted with 3x50 mL $CHCl_3$. These extracts were pooled, dried with anhydrous Na_2SO_4 and, after removal of the drying agent by filtration, the solvent was removed under vacuum. The residual yellow oil was distilled under vacuum, at 150-160 °C at 1.8 mm/Hg, to give a pale yellow product. This was dissolved in a few mL MeOH and neutralized with a solution of fumaric acid in MeOH. The clear solution was heated and diluted with two volumes of hot isopropyl acetate. On cooling, fine white crystals of α,2-dimethyltryptamine fumarate (2,α-DMT) were deposited. These were removed by filtration, and air-dried to constant weight. The yield was 1.64 g (60%) of a product with a mp of 209-211 °C.



DOSAGE: 300 - 500 mg, orally

DURATION: 7 - 10 h

QUALITATIVE COMMENTS: (with 200 mg, orally) "I feel just a little bit intoxicated. Probably few if any effects."

(with 300 mg, orally) "It was an hour before I realized that something was happening. Very subtle, some tingling of the face, the lights are somehow brighter. Really laid back, try to let my fantasy go with closing my eyes and sitting quietly,

but it mostly just felt good to sit quiet. I feel that I am on the edge of something here, but I see it slipping away. "

(with 450 mg, orally) "It was almost as if I had had a drink too many. I was feeling good, but I tried turning the dial on the radio to find music, and the fine motor coordination in my hands was not there. My thinking was completely clear, and the music I finally found was fine for day-dreaming. There were some flashes on the edge of my visual field and things seemed to feel softer and richer. Eating was quite an adventure in tastes, but I really couldn't eat much. Very peaceful, and an easy sleep took over at about the 13th hour. Next day, still pretty dehydrated. All in all, it was a very nice experience."

EXTENSIONS AND COMMENTARY: I do love the satisfying feeling that comes with the successful assignment of a pharmacological change as a function of a single structural change. This is the holy grail of every SAR enthusiast (SAR = Structure Activity Relationship). Make a change in structure, see a corresponding change in activity. There is a correlation. There is causality. And there you have a new, firmly established fact of science to add to the understanding of the universe.

A case in point. What happens when you put a methyl group on the two-position of the indole ring of a tryptamine? In the three examples, examples of the best-studied tryptamines that were not active orally, they all became orally active. DMT, DET and 5-MeO-DMT, the three major parenterally-only active psychedelics, all blossomed into orally active compounds with the addition of a simple methyl group to that indole 2-position. As I had smugly argued in the discussions of 2-Me-DMT, 2-Me-DET and 5-MeO-TMT, it is as if that bit of bulk got in the way of the destructive amine oxidases, and protected the molecule from its expected first-pass metabolic destruction.

So what happens here? You take a compound, α-MT, that is already immune to this oxidase system and is already orally active. Add a 2-methyl group to give 2-Me-α-MT (or 2,α-DMT). And what happens? The potency goes down, not up, and by a factor of 10 times. And it ends up being more of a sedative than a stimulant. It would be neat to take advantage of the chiral center (as with α,O-DMT) and see which optical isomer has the sedative properties.

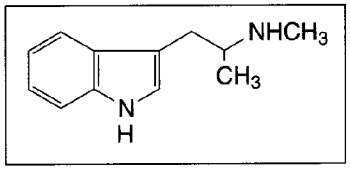
So much for generalities. I suspect that I do not understand the universe nearly as well as I thought I did.

#8. α,N-DMT; TRYPTAMINE, α,N-DIMETHYL; INDOLE, 3-[2-(METHYLAMINO)PROPYL]; α,N-DIMETHYLTRYPTAMINE; 3-[2-(METHYLAMINO)PROPYL]INDOLE; ALPHA-N

SYNTHESIS: (from indoleacetone) To a solution of 1.55 g NaOAc in 5 mL acetic anhydride there was added 2.0 g 3-indoleacetic acid and the mixture was heated at

135-140 °C for 18 h. Removal of all volatiles on the rotary evaporator under vacuum produced a pale yellow residue that was the 1-acetylindole-3-acetone. This was dissolved in MeOH to which 0.93 g MeONa was added, and the solution held a reflux several hours. After removal of the solvent under vacuum, the residue was suspended in H_2O and extracted with several portions of Et_2O. These extracts were pooled, and removal of the solvent under vacuum gave 0.41 g (21%) indole-3-acetone as a white solid, mp 115-117 °C. MS (in m/z): indolemethylene$^+$ 130 (100%); parent ion 173 (16%). IR (in cm^{-1}): 691, 753, 761, 780, 1017, 1110, 1172, and a broad C=O at 1710.

To 1 g shredded aluminum foil there was added a solution of 20 mg $HgCl_2$ in 15 mL H_2O. After 15 min the amalgamated aluminum was drained free of the mercury solution, well washed with fresh H_2O, and shaken as dry as possible. There was then added, in sequence, a solution of 1.5 g methylamine hydrochloride in 2 mL H_2O, 3 mL of 25% NaOH, 5 mL of IPA, and finally 1 g of indol-3-ylacetone in 20 mL IPA. This was stirred for 1 h, then heated briefly on the steam bath. After cooling, the reaction mixture was filtered and the solids washed with MeOH, the washing and filtrate combined, and stripped of solvent under vacuum. The residue was dissolved in 200 mL H_2O, made acidic with HCl, washed with CH_2Cl_2, treated with aqueous NaOH to a pH of greater than 9 (becomes cloudy), and extracted with 2x50 mL CH_2Cl_2. Removal of the solvent from the combined extracts gave a light brown oil which distilled at 125-135 °C at 0.4 mm/Hg to give 0.74 g of a viscous oil. This was dissolved in 5 mL IPA, neutralized with concentrated HCl and diluted with anhydrous Et_2O to the point of turbidity. After standing, the solids were removed, washed with Et_2O and air dried, to yield 0.87 g of α,N-dimethyltryptamine hydrochloride (α,N-DMT) as white crystals. MS (in m/z): $C_3H_8N^+$ 58 (100%); indolemethylene$^+$ 131-130 (19, 14%); parent ion 188, just above noise level.



Alternately, the indol-3-ylacetone can be catalytically reduced in the presence of methylamine. A solution of 3.3 g indol-3-ylacetone in 100 mL EtOH was hydrogenated over Pd-C catalyst in the presence of an excess of methylamine. After 2 h the catalyst was removed by filtration, the filtrate stripped of solvent under vacuum, the residue dissolved in H_2O and made acidic. After washing with Et_2O, the aqueous phase was made alkaline, and the solids that formed were removed by filtration and recrystallized from a mixture of hexane and THF. The product, α,N-dimethyltryptamine (α,N-DMT), was a tan solid that weighed 2.2 g and had a mp of 93-94 °C. The picrate is brick red from EtOH, and melted at 207-208 °C.

(from α-MT) A solution of 4.4 g alpha-methyltryptamine (α-MT) in 5.5 g acetic anhydride containing 3.1 g HOAc and 2.4 g HCO_2H was stirred at room temperature for 18 h. All volatiles were removed under vacuum at a temperature of less than 40 °C which left a syrup as a residue. To this was added 100 mL H_2O and extracted with several portions of Et_2O which were combined and the solvent

removed under vacuum. There remained 4.9 g (95%) of α-methyl-N-formyltryptamine which was used as such in the next step. This was dissolved in 30 mL anhydrous THF and this solution was added to a gently refluxing suspension of 3.7 g LAH in 30 mL THF, under nitrogen, and the reflux was continued for 16 h. After cooling, the excess hydride was destroyed by the careful addition of wet THF followed by sufficient aqueous NaOH to produce a solid that can be easily removed by filtration. After filtration, the filtrate was stripped of solvent under vacuum and the residue (4.3 g) crystallized from benzene/petroleum ether to give 2.5 g (56%) of α,N-dimethyltryptamine (α,N-DMT) as a solid with a mp of 90-91 °C. The N-ethyl homologue, made in a similar way from α-methyl-N-acetyltryptamine, had a mp 187-189 °C.

DOSAGE: 50 - 100 mg, orally

DURATION: 6 - 8 h

QUALITATIVE COMMENTS: (with 50 mg, orally) "Something was going on, and it was rather strong a couple of hours into it, but there doesn't seem to be anything particularly psychedelic here. I am wakeful and alert, maybe a little bit starry-eyed as if I were wearing glasses with the wrong prescription. Maybe a little bit light-headed as well. It was several hours before these physical discomforts disappeared."

(with 75 mg, orally) "Compulsive sneezing, and quite uncomfortable. Urpy. Tried eating some quiche, and couldn't do it—no appetite at all. Pulse seems to be proper, but it is almost as if I were using speed without any of the stimulant virtues. After about three or four hours I am losing the buzziness property and am pretty much normal in three or four more hours. Still some teeth clench. Sleep OK. I'm not sure that going higher is worth it. Or even repeating it. Why?"

EXTENSIONS AND COMMENTARY: The relationship between α-MT (alpha-methyltryptamine) and this compound, α,N-DMT (alpha,N-dimethyltryptamine) is exactly analogous to that seen with the phenethylamine counterparts, between amphetamine (alpha-methylphenethylamine) and methamphetamine (alpha,N-dimethylphenethylamine). Both the primary and the secondary amine compounds retain activity. In the amphetamine camp, both compounds are dramatic stimulants showing a complete spectrum of sympathomimetic properties including cardiovascular excitement, loss of appetite, and sleeplessness. Here, the tryptamine counterparts are similar to one another, but it is not as clear that they are stimulants. In animal studies, they have been compared with each other and with amphetamine. Except for the speed of onset, both tryptamines caused amphetamine-like behavior in activity cages, but required some 10 times the dosage of amphetamine. In man there are some suggestions of this, the loss of appetite, the buzzy lightheadedness, and the absence of any of the usual suggestions of psychedelic action.

I mentioned an appealing hypothesis in the commentary on α-MT, and it is applicable here. Both of these materials, α-MT and α,N-DMT, are effective monoamine oxidase inhibitors. Both of these materials show some of the syndrome that has been described for the monoamine oxidase inhibitors of the beta-carboline family. It would be interesting to design and conduct a study into the role that either of these might play in promoting the oral activity of the materials of ayahuasca that are deaminated and thus deactivated when taken alone. This entire argument could and should embrace the methoxylated counterpart, α,N,O-TMS. I am not aware of any studies that have been made as to its deaminase enzymatic effectiveness, but it too fulfills that nausea, discomfort, un-psychedelic pattern shown here. The expected increase in potency due to the 5-methoxy group is proper, making it a more potent compound than either of these two. It has its own entry.

In all of these cases, the adding of an additional methyl group to the nitrogen atom makes a tertiary amine. In the phenethylamine analogy, one gets N,N-dimethylamphetamine. This compound appeared in a couple of clandestine methamphetamine laboratories a few years ago, as a result of the cooks substituting N-methylephedrine for the customary precursor, ephedrine. Although animal studies on N,N-dimethylamphetamine showed it to have little if any stimulant properties, the authorities reasoned that since it had appeared in an illicit context (potentially being peddled as a street drug) it had a real abuse potential. And since it had no recognized medical utility, its obvious resting spot was in Schedule I of the Controlled Substances Act. And there it was, indeed, placed.

The application of this structural modification to the tryptamine area gives alpha,N,N-trimethyltryptamine (α,N,N-TMT). The tertiary amine in the phenethylamine, N,N-dimethylamphetamine, showed a loss in its stimulant nature. Here, the adding of that additional methyl group gives a tertiary amine that has the skeleton of DMT. This base has been reported as having been made by either of two different routes, both starting with indole. Reaction with propyleneoxide gave the 1-(indol-3-yl)-2-propanol which was treated first with PBr_3 followed by dimethylamine. Or, reaction with chloropropionyl chloride gave a 1,3-bis intermediate which was converted to the amino ketone 3-[2-(dimethylamino)propionyl]-indole with dimethylamine. This was reduced to the same product, α,N,N-TMT, with LAH. The bimaleate salt had a mp of 139-140 °C.

Another parallel exists between the amphetamine world and the tryptamine world. Rather than adding a second methyl group to the terminal nitrogen, simply keep the one methyl group that is there and lengthen it by another carbon atom. Make the methyl into an ethyl. With the amphetamine/methamphetamine prototype, this extension provides the homologue N-ethylamphetamine and by further extension, N-propyl, N-butyl, N-etc. amphetamines. With the same manipulation, again in the phenethylamine world where there is a 3,4-methylenedioxy substitution on the aromatic ring, one gets the MDA, MDMA, MDE, MDPR series of compounds. The exact same world exists with the tryptamines. Lengthening the N-methyl group of α,N-DMT leads to compounds that are known and potentially

active in man, but which have not yet been explored. As discussed under DPT, the presence of two different alkyl groups on a tryptamine are best named for those two groups, with their locations given as numbers or letters as prefixes in front of the initialed code. But here the convention becomes hopelessly ambiguous. What is to be done if one of the prefixes belongs to one group, and the other to the other? One has to break them up, of course. But then something else like α-M-N-ET becomes a nightmare to be properly located in the long index. Let's compromise with α-MET, where the M belongs to the α, but the E (ethyl) is on the T (tryptamine) nitrogen atom where it belongs. So, the N-ethyl compound (alpha-methyl-N-ethyltryptamine) becomes α-MET and it forms readily through the reductive alkylation of indol-3-ylacetone with ethylamine (HCl salt, mp 187-189 °C, picrate mp 203-205 °C), and the N-isopropyl analogue (alpha-methyl-N-isopropyltryptamine) becomes α-MIPT and it results from the reductive alkylation of indol-3-ylacetone with isopropylamine (HCl salt, mp 229-230 °C, picrate mp 219-220 °C). Their pharmacology in animals is not exciting, but they are untried in man. Well, maybe they are untried. An early patent (1962) that gives the synthesis for both the N-methyl and the N-ethyl compounds (α,N-DMT and α-MET) claims that they both have psychostimulant properties.

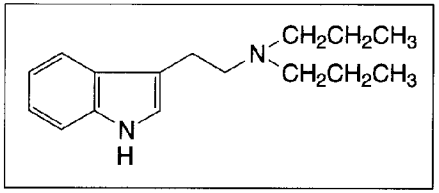
And, as a final note, be careful. The code TMT has two meanings. In the phenethylamine area it identifies the mescaline analogue, 3,4,5-trimethoxy-tranylcypromine (or trans-2-(3,4,5-trimethoxyphenyl)cyclopropylamine). This is entry #56, page 607 of *PIHKAL*, and check there for further details. Here, entries of trimethylated tryptamines will be preceded by the specific locations of the methyl groups prefixes with numbers, Greek letters, and/or N for nitrogen.

#9. DPT; TRYPTAMINE, N,N-DIPROPYL; INDOLE, 3-[2-(DIPROPYLAMINO)ETHYL]; N,N-DIPROPYLTRYPTAMINE; 3-[2-(DIPROPYLAMINO)ETHYL]INDOLE

SYNTHESIS: (from tryptamine) A solution of 1.6 g tryptamine base in 10 mL IPA was treated with 5.1 g propyl iodide and 5.2 g diisopropylethyl amine, and stirred at room temperature for 36 h. The volatiles were removed under vacuum, and the residue was partitioned between CH_2Cl_2 and H_2O made basic with NaOH. The organic phase was separated, the aqueous phase extracted with two additional portions of CH_2Cl_2, the extracts pooled and the solvent removed under vacuum. The residue, a fluid brown oil weighing 2.75 g, was treated with 5 g acetic anhydride and heated on the steam bath for 20 min. After cooling, a small amount of ammonium hydroxide was added, and the mixture added to 200 mL 0.5 N H_2SO_4. This aqueous solution was washed three times with CH_2Cl_2 and then made basic with 25% NaOH. This was extracted with 3x40 mL CH_2Cl_2, the extracts pooled,

and the solvent removed under vacuum. The oily residue was distilled at 145-155 °C at 0.08 mm/Hg to give 1.14 g N,N-dipropyltryptamine base as a white oil. This was dissolved in 5 mL IPA, acidified with concentrated HCl, and diluted with 20 mL anhydrous Et_2O to give N,N-dipropyltryptamine hydrochloride (DPT) as a fine white powder. Yield was 1.10 g (39%) with a mp of 174-176 °C. IR (in cm^{-1}): 759, 774, 831, 987 (br.), 1084, 1101. The replacement of the organic base diisopropylethyl amine with an equivalent amount of $NaHCO_3$ yielded the same product but with a yield of less than 10%.

(from indole) To a well-stirred solution of 10 g indole in 150 mL anhydrous Et_2O there was added, dropwise over the course of 30 min, a solution of 11 g oxalyl chloride in 150 mL anhydrous Et_2O. Stirring was continued an additional 15 min during which time there was the separation of indol-3-ylglyoxyl chloride. This intermediate was removed by filtration and used directly in the following step. This was added, in small increments, to 20 mL anhydrous dipropylamine which was being stirred. There was then added an excess of 2N HCl, the mixture cooled, and the resulting solids removed by filtration. These were recrystallized from aqueous EtOH to give, after air drying, 13.2 g indol-3-yl-N,N-dipropylglyoxylamide, mp 95-96 °C. A solution of 13 g indol-3-yl N,N-dipropylglyoxylamide in 350 mL anhydrous dioxane was added, slowly, to 19 g LAH in 350 mL dioxane which was well-stirred and held at reflux temperature under an inert atmosphere. After the addition was complete, refluxing was maintained for an additional 16 h, the reaction mixture cooled, and the excess hydride destroyed by the cautious addition of wet dioxane. The formed solids were removed by filtration, washed with hot dioxane, the filtrate and washings combined, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum. The brownish residue was dissolved in anhydrous Et_2O and saturated with anhydrous hydrogen chloride. The resulting crystals were recrystallized from benzene/methanol to give 11.9 g (49%) of N,N-dipropyltryptamine hydrochloride (DPT) with a mp of 178-179 °C.



DOSAGE: 100 - 250 mg, orally

DURATION: 2 - 4 h

QUALITATIVE COMMENTS: (with 200 mg, orally) "This started sooner and was a lot stronger than I had expected. I had trouble talking and I felt very uncomfortable. I think physically I was in a chair but I was on a kind of mountain surrounded by clouds. And the clouds talked to me."

(with 250 mg, orally) "I was seeing the Light real strongly. The Light sort of looked like bright bursts of Light but also like a kind of Spiritual Tunnel, and it

seemed at one point, along with that, I saw a Human form, but the Vision seemed like I was sort of inside the Being and outside, and the Human was inside me and appeared to be outside, but I didn't see the being's face or clearly see the various limbs because the Being seemed to be the tunnel of Light that I was inside in the Vision, and seemed much larger than me. As King Jesus said: (St. John 6:56) 'Whoever eats my Flesh and drinks my Blood lives in me and I live in them.'"

(with 275 mg, orally) "I have smoked this amount one time some while ago, and this is a lot more interesting. And a lot more intense. With smoking, there was a body rush that was uncomfortable, and you never really know how much went into you, what with pyrolysis and all."

(with 500 mg, orally) "This was intensely visual, and it lasted an exhausting 12 hours. I prefer the smoking route."

(with 100 mg, smoked) "The entire experience lasted only 20 minutes. I found the visual experience to be everything. It was a lot more benign than mushrooms with pretty much no toxic things, more like mescaline."

(with many mg, smoked) "I saw this vision of two hearts rotating. They were shaped like the usual heart shape (like a valentine). They filled most of my vision and were rotating one inside the other. Around the outside of the hearts there were sparkling jewels or crystals of light of different colors, maybe four rows deep surrounding them all around. This vision was totally clear. When I saw this vision, time was very full and long and complete."

(with 80 mg, intramuscularly) "I feel light and nervous. I'm way off in a big castle with beautiful colors and scenery. I'm back with the girl who accused me of fathering her child. It's peaceful. She had everything she wanted. My aunt made sure we went to church on Sunday. I see the devil in front of my face. Everything is going fast. Too fast. It's not pleasant. Things are going zig-zag. Feels like I'm tired. I feel like an old man in a rocking chair sitting in front of a phonograph. Everything is so mixed up. I'm trying to get myself together. I have a vibrating feeling. It makes me feel as though I'm not here."

(with 100 mg, intramuscularly) "I was being led by the hand of a wise old man who I know was God, and we went off to the front of the synagogue. I was handed a Torah for me to carry as a sign that I had been accepted, and forgiven, and that I had come home."

(with 12 mg, intravenously.) "We were using an i.v. drip with sodium ascorbate which affected the timing, of course. This was strong at this level. I was set to go to a target dosage of 60 milligrams, but decided to stop at 12. It was strong, real strong."

(with 36 mg, intravenously) "This was administered as a sterile solution of the fumarate salt, so the actual weight of the drug used is somewhat less. This was a very intense experience, every bit as powerful as this amount of DMT."

EXTENSIONS AND COMMENTARY: The earliest reports of human activity, at 1 mg/Kg, are mentioned under DMT. The clinical trials, from which the 80 mg

comment above was entered, were conducted on a population of physically sound alcoholics. It was not only a study to define the nature of action of DPT, but to challenge the idea that the metabolism of the dialkyltryptamine on the 6-hydroxyl position might give rise to active metabolites. This challenge was in the form of assaying 6-fluoro-N,N-diethyltrypamine in the same subjects, to see if it might be an active placebo. This is discussed under that specific compound, DET. Incidentally, the actual amount of DPT used was originally published as being 1.0 mg/Kg body weight, and I am guessing that the subject might have been of average weight, about 175 lbs. In these studies, dosages were taken up to as high as 1.3 mg/Kg, which resulted only in a prolongation, not an intensification, of effect. In all trials, the onset of effects occurred between 10 and 15 minutes following injection.

Studies using lower dosages of DPT (15-30 mg intramuscularly) have been explored as adjuncts to psychotherapy with alcoholic patients. The enhancement of recall of memories and experiences, the greater emotional expressivenes and self-exploration, coupled with a consistently short duration, made the drug very attractive. Higher doses, up in the 100 milligram range, have been explored in psychotherapy, in the quest for peak experiences. In yet another study, exploring the interaction of therapy counseling and DPT-induced peak experiences with patients who are dying, the i.m. dosage range was between 75 and 125 milligrams.

There is a rather remarkable religious group known as the Temple of the True Inner Light, in New York City, which has embraced as its Eucharist DPT, which they refer to as a powerful Angel of the Host. Their communion is confirmed by either the smoking or the drinking of the sacrament, and they have been totally unbothered by any agency of the Federal Government, as far as I know. It is not as if they were unknown. Quite on the contrary, I had on one occasion received a request for information on the drug from a reporter who was writing a story on DPT and its use in the church. I asked him just how he had gotten my name, and he told me that he was given it by someone within the DEA. Someone, sometime, should write an essay on contemporary religions, as to why DPT has flown, why peyote forever struggles, and LSD and marijuana have bombed out, when tied to religion. Is there something about a faith being an "approved" religion? Who gives his approval? Who decides the applicability of the first amendment, which explicitly states that "Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof"?

I wish the True Inner Light congregation Godspeed, if you will excuse the expression. My impressions of them from our correspondence have left me totally convinced of their integrity and dedication. It is an intriguing fact that this tryptamine was commercially available for a while from at least one small independent supplier of chemical novelties, but I believe that this is now no longer a valid source.

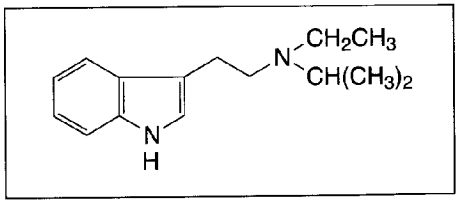
An intriguing (and perhaps theoretical) homologue of DPT is the 1-propyl counterpart, 1,N,N-tripropyltryptamine, referred to as PDPT. It has been claimed that simply reacting tryptamine with an excess of propyl bromide put an alkyl group

on the indolic 1-position (as stated also for the ethyl counterpart, sometimes referred to as EDET). In my own experiments with this reaction, I have yet to see any suggestion of 1-alkylation.

#10. EIPT; TRYPTAMINE, N-ETHYL-N-ISOPROPYL; INDOLE, 3-[2-(ETHYLISOPROPYLAMINO)ETHYL]; N-ETHYL-N-ISOPROPYL-TRYPTAMINE; 3-[2-(ETHYLISOPROPYLAMINO)ETHYL]INDOLE

SYNTHESIS: (from indole): To a well-stirred solution of 1.6 g indole in 30 mL anhydrous Et_2O there was added, dropwise over the course of 30 min, a solution of 3.8 g (2.6 mL) oxalyl chloride in 30 mL anhydrous Et_2O. Stirring was continued for an additional 15 min during which time there was the separation of indol-3-ylglyoxyl chloride as a crystalline solid. This intermediate was removed by filtration and washed with Et_2O. It was used directly in the following step. This solid acid chloride was added to 3.6 g anhydrous ethylisopropylamine in Et_2O, followed by the addition of an excess of 2N HCl. The mixture was cooled, and the resulting product, N-ethyl-N-isopropylindol-3-ylglyoxylamide, was removed by filtration. The air-dried product weighed 2.2 g (62% yield) and had a melting point of 149-151 °C.

A solution of 2.0 g N-ethyl-N-isopropylindol-3-ylglyoxylamide in 50 mL anhydrous THF was added, dropwise, to 1.5 g LAH in 50 mL anhydrous THF which was well-stirred under an inert atmosphere. This was brought to reflux and held there for 3 h. The reaction mixture was cooled, and the excess hydride destroyed by the cautious addition of wet THF. A 15% NaOH solution was then added until the solids had a loose, white cottage cheese character to them, and the mobile phase tested basic by external damp pH paper. These formed solids were removed by filtration, washed first with THF and then MeOH. The filtrate and washings were combined, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum. The residue set up to a crystalline mass weighing 1.6 g (90%). This was recrystallized from pentane to provide N-ethyl-N-isopropyltryptamine (EIPT) as a free base with a mp of 71-73°C. Indole can also serve as a precursor to NET, which is easily transformed into EIPT.



(from N-ethyltryptamine, NET): To a solution of 0.33 g N-ethyltryptamine base (see NET recipe) in 4 mL IPA there was added 1.5 g isopropyl iodide and 1.2 g diisopropylethylamine, and this was held at reflux for 36 h. The volatiles were removed under vacuum, and to the residual black oil there was added 100 mL 15% aqueous NaOH. This was extracted with 3x50 mL CH_2Cl_2, the extracts pooled, the

solvent removed, and the residue distilled at the KugelRohr to give 0.24 g (59%) of N-ethyl-N-isopropyltryptamine as a pale amber oil, bp 150-160 °C at 0.11 mm/Hg, that did not crystallize. MS (in m/z): $C_6H_{14}N+$ 100 (100%); C_3H_8N+ 58 (58%); indolemethylene+ 130 (11%); parent ion 230 (1%). This base was converted to the hydrochloride salt, as described above.

DOSAGE: 24 - 40 mg, orally

DURATION: 4 - 6 h

QUALITATIVE COMMENTS: (with 24 mg, orally) "There is something strange going on, and I am feeling quite urpy, but I feel quite horny at the same time. What would it be like to be making love and vomiting at the same time? Something is not at peace with itself. No way. And then suddenly I am baseline, and there is nothing left."

(with 40 mg, orally) "I see some similarities with DET and MIPT orally, not too pleasant with somewhat dysphoric components and visual effects more in the background. Michael Valentine Smith described a 'little elephant' as a thing to be found in 5-MeO-DMT. And a little of this is to be found in this drug."

(with 40 mg, orally) "Within a half hour, I have sparkling and a very unsure tummy. This is, on one hand, strangely not erotic, and yet I am completely functional, sexually. Remarkable orgasm. But still not erotic. No visuals, no sound enhancement, no fantasy, so why is it up there at a plus 2? I don't know, and I am pretty much baseline by the fifth hour."

(with 40 mg, orally) "In an hour, a very mild pre-nausea, which passed off in about 45 minutes. No visual effects at all. The dreams that night weren't quite as satisfying as the excellent, nice, clear, pretty dreams with an earlier 30 mg trial. The night was full of chopped-up sleep, since I was up about once an hour to pee. Observation: there is some diuretic component to this material. Barely plus 1. Would not bother taking it again."

EXTENSIONS AND COMMENTARY: Clearly this is not an exciting compound. So why go to the extensive bother to make it and test it? For the single reason that the diisopropyl analogue is totally weird, one of the two weird tryptamines that need to be explored. If everything went as predicted, then nothing would ever be discovered. One must look always for the aberration that will demand that you change your working hypotheses and become responsive to unexpected and unexplainable things. 5-MeO-DET has an unexpected property, a lightheadedness and vertigo at a very small dosage. This may prove to be its value in research, and this is discussed in its own entry. Here is a response to another unexpected observation. N,N-diisopropyltryptamine causes extraordinary auditory distortions. What about this molecule does this thing? Are both isopropyl groups needed? Is only one needed? Might neither be needed, but simply to have something equally

massive stuck to that nitrogen atom? This compound, EIPT, is an essential brick in this wall that will contain, define, and describe the fine details of this remarkable CNS property.

This is why EIPT is interesting. Let me itemize these close relatives of the diisopropylamine analogue, maintaining one isopropyl group but letting the other be something different. What can be seen from all of this exploration?

N1	N2	name	action
methyl	isopropyl	MIPT	It seems to be psychedelic in the 25 mg area, but it has not been brought up to the 40 mg level.
ethyl	isopropyl	EIPT	An uncomfortable nausea and uncomfortable trip, but no auditory disruptions.
propyl	isopropyl	PIPT	(not yet evaluated)
isopropyl	isopropyl	DIPT	Intense auditory distortion at the 40 mg level.
butyl	isopropyl	BIPT	(not yet evaluated)

If it turns out that the diisopropyl substitution is an absolutely essential structural component of this sensory phenomenon, then it will become one of the most remarkable tools known for the study of the human auditory association area in the brain.

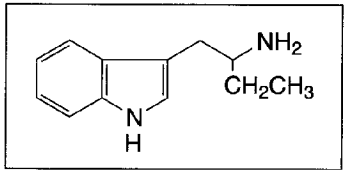
This is why all of this research is important. You can never tell what a new compound will do. So you must continue to make new compounds and you must continue to be the observer. It is truly an exciting world.

#11. α-ET; ALPHA-ETHYLTRYPTAMINE; INDOLE, 3-(2-AMINOBUTYL); TRYPTAMINE,ALPHA-ETHYL; 3-(2-AMINOBUTYL)INDOLE; ETRYPTAMINE; MONASE

SYNTHESIS: To a 50 °C warmed mixture of 60 mL glacial acetic acid and 18 mL acetic anhydride, there was added 66 g crystalline ammonium acetate, and stirring continued until solution was complete (20 min). To this there was added a solution of 87 g indole 3-carboxaldehyde (see under α-MT for preparation) and 300 mL nitropropane in 360 mL acetic acid. The mixture was held at reflux temperature for

3 h, cooled, and diluted with 360 mL H_2O. After standing at 10 °C for several additional hours, the solids were removed by filtration and recrystallized from 600 mL of 40% EtOH to give, after filtering and drying to constant weight, 44.5 g of 1-(3-indolyl)-2-nitrobut-1-ene-1 (α-ethyl-β-indoleninidenium ethyl nitronate) which had a mp of 128-131 °C. Anal. ($C_{12}H_{12}N_2O_2$); C: calcd, 66.64; found 67.54: H,N.

A suspension of 31.7 g LAH in 300 mL anhydrous THF, stirring under an inert atmosphere, was treated by the addition of a solution of 36 g 1-(3-indolyl)-2-nitrobut-1-ene in 285 mL anhydrous THF. This was added dropwise over the course of 3 h, while the mixture was being brought up to reflux temperature. The reaction mixture was held at reflux for an additional 2 h, then allowed to return to room temperature. After standing overnight, the excess hydride was destroyed by the cautious addition of 500 mL wet Et_2O, followed with 70 mL H_2O, 100 mL THF, and finally 20 mL 50% NaOH. After 1 h additional stirring, the solids were removed by filtration, washed with 1.5 L Et_2O, the combined filtrate and washings dried over anhydrous K_2CO_3, and the solvent removed under vacuum. The residue, 78 g, was dissolved in 100 mL MeOH, treated with 12 mL acetic acid, stripped of volatiles under vacuum, redissolved in a mixture of 250 mL ethyl acetate and 30 mL MeOH, concentrated to a volume of about 100 mL, and again treated with 2 mL acetic acid. The product, α-ethyltryptamine acetate (α-ET), separated as a solid with a mp of 164-165.5 °C. Anal. ($C_{14}H_{20}N_2O_2$); H: calcd, 8.11; found 7.60: C,N. It can be recrystallized from ethyl acetate/MeOH, which increased and tightened the mp to 165-166 °C. The free base, from ethyl acetate/petroleum ether, had a mp 97-99 °C. The hydrochloride salt has a mp 215.5-218 °C. The picrate had a mp 165-166 °C.



DOSAGE: 100 - 150 mg, orally

DURATION: 6 - 8 h

QUALITATIVE COMMENT: (with 50 mg, orally) "No effects of any kind were felt with 50 milligrams, orally."

(with 100 mg, orally) "A nearly imperceptible feeling of well-being and pleasure was noted about 80 minutes later, and seemed completely gone at three hours."

(with 105 mg, orally) "Very slowly soluble in water and mildly bitter. I was aware of something just before a half-hour, and at one hour I had a light-headed sparkle and felt light of body. It is like speed without the cardiovascular, or like a psychedelic without the visuals. I can see how it was sold in Chicago as MDMA. At two hours, a slight cooling of the feet, a bit of unsureness in the gut, a tendency to squeeze the teeth together, a trace of eye-wiggle, and a tendency to talk with my ears popped. Four and a half hours, largely out, with some residue in eyes and teeth.

Six hours baseline, and fine sleep. No residue."

(with 110 mg, orally) "I am in a very different place. It's exciting but at the same time I don't know what to do with the energy. It makes my eyes want to close."

(with 120 mg, orally) "Very keen, pure euphoria, feels great. Reaches +3 in about one hour. Sharply focused feelings very strong, strong energy push. Keeps rising until it goes over the top and begins to break up. The pure tone of euphoria gets joggled with other feelings, like a bit too much to handle. Not really uncomfortable, but not as nice as the earlier +2 stage. A wall seems to grow around me. I am being shut off from intimate contact with others. But in a couple of hours the push of the drug diminishes, and I get more comfortable. The day ended beautifully."

(with 130 mg, orally) "There was a smooth onset of relaxation at about 55 minutes with only a trace of motor intoxication. Both radio and television seemed more enjoyable than normal and there was a definite enhancement of the beauty of instrumental music. The effect seemed to peak at about 150 minutes and was essentially gone at the five hour point. There were never any visuals nor any type of sensory distortions, just warm, pleasant feelings. No interference with sleep was noted, and there were no after-effects the next day."

(with 150 mg, orally) "My dosage level was the highest of the group, but, to my surprise, it had almost no effect whatsoever. A plus-one, if anything. After the peak, as I was slowly coming down, I was aware of feeling slightly depressed. This state continued until I achieved baseline, but was not severe enough to prevent me from participating in the general good spirits of the group. There is a real possibility that my weekly use of MDMA for writing might have built up a tolerance to the stimulation of this material. I think that that may be close to the answer. Would I take it again? Not with much enthusiasm. It didn't give enough exciting rewards."

(with 160 mg, orally) "A strong feeling of being-at-peace was evident in an hour, although there was some concentration required to do things in a coordinated way. I wouldn't want to drive a car. There seemed to be very easy drifting of thoughts but no visuals or sensory distortions. There were no GI disturbances anywhere along the line except for some loose stools the next morning. Appetite was slightly depressed, but food tasted very good. Sex at the 2-hour point showed some difficulty in reaching orgasm but significantly enhanced pleasure during orgasm once it was attained. A very slight tremor could be detected in the fingers around the peak of the experience. There was a desire to talk with friends somewhat reminiscent of MDMA; I am sure that this drug could be quite a social-enhancing material. The effects wore off gradually and were essentially gone by the six hour point. Sleep was unaffected; however, the next morning there was a slight feeling of dullness and possibly hang-over which quickly wore off."

EXTENSIONS AND COMMENTARY: This base, α-ET or etryptamine, was a

promising anti-depressant, explored clinically as the acetate salt by Upjohn under the name of Monase. Its central stimulant activity is probably not due to its monoamineoxidase inhibition activity, but appears to stem from its structural relationship to the indolic psychedelics. It was withdrawn from potential commercial use with the appearance of an unacceptable incidence of a medical condition known as agranulocytosis, but the extramural research into its action, among the lay population, goes on.

One property has been mentioned more than once in anecdotal reports. It appears to serve well, with short term dosage regimens, as an effective tool in kicking dependency on opiates. In chronic use, there is a rather rapid tolerance built up over four or five days, that allows a dosage escalation to a daily load of a gram or more. There might be some discomfort such as sores in the softer tissues of the mouth, but apparently the withdrawal from heroin is easy and effective. Here is a potential tool in addiction treatment that might warrant closer investigation.

Other homologues of α-ET have been synthesized. The α-propylhomologue (α-PT) has been made from tryptophan, and the acetate salt was recrystallized from ethyl acetate/MeOH and melted at 158-158.5 °C. It has not, to my knowledge, ever been tasted. But I suspect that it will take a pretty hefty dosage to get some CNS effect based on the loss of potency with the similar homologation in the Muni Metro series related to MDMA. Rather than lengthening the chain on the alpha-position, some studies have exploited the known potency enhancement that comes from putting a methoxyl group on the 5-position of the indole. This compound, 5-MeO-α-ET, has been made from the 5-methoxyindole-3-aldehyde by coupling with nitropropane (with ammonium acetate) to form the nitrobutene which is a reddish, crystalline material, mp 114-116 °C from ethanol. LAH reduction in Et_2O/THF gave the desired 5-MeO-α-ET in a 72% yield, mp 201-203 °C, as the hydrochloride salt. There is an alternate synthesis that avoids LAH which involves the conversion of 5-methoxyindole to the nitrobutane with 2-nitro-1-butene, followed by reduction with nickel boride to give 5-MeO-α-ET, as the free base in a 52% yield, mp 110-112 °C. As might have been predicted, it was more potent than α-ET by a factor of two with 70 milligrams orally producing a trippy feeling that lasted several hours accompanied with an increased heart beat and difficulty in sleeping. There were no psychedelic effects as such, and no unpleasant side effects. Another compound that has been closely associated with α-ET is a carboline. If a molecule of acetone is brought to react with the amine group and the indolic 2-position, in a condensation that is called a Pictet-Spengler reaction, there will be formed 1,1-dimethyl-3-ethyl-1,2,3,4-tetrahydro-β-carboline. This is a chemical ally of the harmine family of alkaloids, but I have not heard of its having been explored psychedelically. It has been reported to be an impurity of commercial α-ET (including the pre-scheduling product from the Aldrich Chemical Company) to an extent of some 30%. At these levels, it was suggested that it might play some role in the central action of the parent tryptamine.

α-ET has played yet another role in the evolution of our drug laws, a role

that will be found to be of extraordinary importance once it becomes more widely known. This compound may prove pivotal in our ultimate definition of the Analogue Drug Law. I want to talk about: (1) The Controlled Substance Analogue Drug Bill; (2) What happened in a trial in Denver; and (3) What happened in a District Court in Colorado.

During the most political period of the War on Drugs Congress passed and the president signed a new law every two years, on the even-numbered years (the years of congressional re-election), that increased either the definition of what were illegal drugs, or the penalties that follow a conviction for having been associated with them in any way. In 1986, there was a proposed draft of a bill called the "Designer Drug Bill" that had been created within the DEA, and sent on to the Justice Department who, in turn, submitted it to Congress as desired legislation. This was a proposal that would make it illegal to tinker with the structure of a molecule of an illegal drug, to change it in a way that would make it fall outside of the explicit listings of illegal drugs but without significant changes in its pharmacological effects. It was the first time a drug law would define a crime by the activity of a compound as well as by chemical structure. The proposal went to the appropriate legislative committee and, with some modifications, it became law in 1986. There was considerable celebration within the DEA, expressing a "We did it!" kind of satisfaction.

The first three Articles of the Constitution of the United States are entitled: Article. I. The Legislative Department; Article. II. The Executive Department; and Article. III. The Judicial Department. The first of these consists of Congress, which has the role of writing law and defining the military structure of the nation. The second of these defines the president, who approves the laws of Congress and is the highest military officer. The third of these is invested in the enforcement of these laws. The three departments were defined in a way to assure a balance of power. It is a dangerous step towards a totalitarian state when one special interest group (here the DEA) can, in effect, both write the law and then enforce it.

(1) The Controlled Substance Analogue Drug Bill. This is contained within Public Law 99-570, the Controlled Substances Analogue Enforcement Act of 1986. This is the so-called "Designer Drug" bill which was intended to allow the prosecution of any act associated with an unscheduled drug, if that drug is analogous either in structure or in action to a scheduled drug, and if it is intended for use in man. Here is the exact wording of this amendment:

> (32)(A) Except as provided in subparagraph (B), the term 'controlled substance analogue' means a substance —
>
> "(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;
>
> (ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulent, depressant, or hallucinogenic effect on the central

nervous system of a controlled substance in schedule I or II; or

"(iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II.

"(B) Such term does not include —

"(i) a controlled substance;

"(ii) any substance for which there is an approved new drug application;

"(iii) with respect to a particular person any substance, if an exemption is in effect for investigational use, for that person, under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) to the extent conduct with respect to such substance is pursuant to such exemption; or

"(iv) any substance to the extent not intended for human consumption before such an exemption takes effect with respect to that substance.".

"SEC. 203. A controlled substance analogue shall, to the extent intended for human consumption, be treated, for purposes of this title and title III as a controlled substance in schedule I.".

This is the exact wording of the law, and I have discovered that the more times I read it the more convinced I become that, whatever the original intent might have been, it was structured in a way to promote vagueness. I have written elsewhere about the rhetorical nightmare of a double disclaimer, "substantially similar." "Similar" means "pretty much the same." "Substantially identical" would means "pretty much the same." But what does "substantially similar" mean? I like the analogy of seeing two cut glass shakers in the center of the fancy table, one with small holes in the silver screw-down cap containing salt, and the other with slightly larger holes containing pepper. Are these two items substantially similar? If you happen to be a collector of antique crystal glassware, these items are completely identical. If you happen to need to add a condiment to your entree these items are totally different. You must know whose eyes are being looked through to approach the question of "substantial similarity." At a trial a few years ago in Southern California the issue was settled once and for all for a confused jury when a forensic chemist gave an expert opinion that two things were substantially similar when they were greater than 50% identical. Is the right hand more than 50% identical to the right foot? This opinion was patently absurd.

(2) What happened in a trial in Denver? A few years ago a young man

discovered that the Aldrich Chemical Company offered alpha-ethyltryptamine acetate as a fine chemical. He could buy it in 100 g quantities, and package it in 150 milligram capsules to be sold to the street trade as Ecstasy, or MDMA. He could and he did. His actions came to the attention of Law Enforcement, and an opinion was obtain from a DEA chemist that α-ET was not an analogue substance. So the prosecutor decided against pressing charges. But not every one agreed with this not-analogue opinion.

So the chemist solicited the thoughts of his professional colleagues and the answers came back with as many no's as yes's. The no's were from those who reasoned objectively (scientific, compare the structures) and the yes's were from those who reasoned subjectively (abuse potential, compare the action).

The adventurous α-ET peddler continued, and was again brought to task. The analytical duties went to another chemist, and charges were finally brought under the Analogue Drug Bill. But the earlier opinion was in the record, and the first chemist was brought in by the defense to present these findings at the trial. Clearly there was uncertainty if this was an analogue of anything that was scheduled. The research toxicologist for the home-office of the DEA gave testimony that it was, without question, an analogue. But on cross examination, he was asked just how many times, and for for how many different drugs, he had been asked that same question, as an expert witness at a criminal trial. Perhaps twelve, he said. And how many times had he offered the conclusion that the proposed compound had been an analogue of a scheduled drug? In every case. The judge decided that there were some conflicting opinions here, amongst the experts, and dismissed the charges. The defendant was given the warning that this kind of leniency was not common, and told to behave himself in the future.

(3) The text of the appellate decision in this matter is a valuable lesson in the fine aspects of grammatical analysis. This all is from 806 F.Supp. 232 (D.Colo., 1992). In way of background it emphasizes that the purpose of the controlled substance analogue statute is to attack underground chemists who tinker with molecules of controlled substances to create new drugs that are not yet illegal. In this case, the defendants were not chemists who created or marketed a designer drug but rather allegedly purchased and distributed a substance that preexisted drugs to which it was a purported analogue. This was probably, in and of itself, sufficient reason to deny the appeal. But the argument developed marvelous new texture as things progressed. As a reminder of the wording of the law (here SS is, of course, substantially similar but this terminology is not addressed in the decision), the three phases of the definitional part of the law can be summarized as follows:

	(i)	a chemical structure which is SS to ... ;
	(ii)	which has an effect that is SS to ... ;
or	(iii)	which is represented as having an effect that is SS to ...

The prosecution's reading and analysis of this definition:

"The government's reading of the analogue definition has superficial appeal. As a matter of simple grammar, when an "or" is placed before the last term in a series, each term in the series is usually intended to be disjunctive. Under this reading, α-ET would be an analogue if it satisfies any of the three clauses; however, this reading ignores other grammatical principles that apply in favor of defendant's construction. The operative segments of clauses (ii) and (iii) both begin with the word 'which,' signaling the start of a dependent relative clause modifying a previous noun. In each case the precedent noun is 'chemical structure' found in clause (i). Because both clauses (ii) and (iii) can be read to modify clause (i) the statutory language can be fairly read as requiring the two-pronged definition asserted by the defendants."

The defendant's reading and analysis of this definition:

"Defendant's reading is also bolstered by a deeply rooted rule of statutory construction. A statute must be construed to avoid unintended or absurd results. If I adopt the government's construction and read clause (ii) independently, alcohol or caffeine would be controlled substance analogues because, in a concentrated form, they can have depressant or stimulative effects substantially similar to a controlled substance. Likewise, if I read clause (iii) independently, powdered sugar would be an analogue if a defendant represented that it was cocaine, effectively converting this law into a counterfeit drug statute. In both cases the defendant could be prosecuted for selling a controlled substance analogue even though the alleged analogue did not have a chemical structure substantially similar to a schedule I or II controlled substance. Therefore, to prevent this unintended result, clause (i) must apply to any substance that the government contends is a controlled substance analogue."

There is a most instructive bit of history to be considered. In July, 1986, the House of Representatives considered the Designer Drug Enforcement Act of 1986 (H.R. 5246). As with the Senate, the House bill focused on underground chemists who seek to evade the drug laws by slightly altering a controlled substance. The House proposed a two-pronged definition of "analogue" that is virtually identical to the construction advocated by the defendants here. The House bill contained the same three clauses as the current statute, but added the word "and" after clause (i). Congress ultimately adopted the analogue statute as part of the comprehensive "Anti-Drug Abuse Act of 1986." Inexplicably, the analogue definition enacted by Congress dropped the word "and" after clause (i).

This pretty well defines the legislative intent of Congress, and I would give a pretty penny to meet the writer who happened to delete that "and," the one critical word that changed the heart of the law. I would like to know to whom he answered.

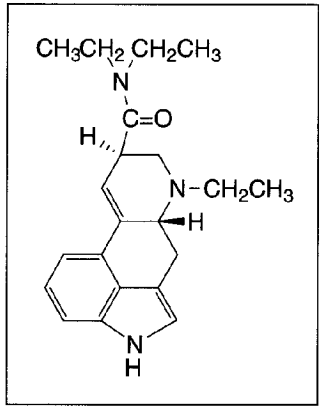
Here is a masterpiece of logic which makes some sense out of sloppy law. It must be remembered that the purpose of all of this is to determine if one, or two, or three definitions must be applied to establish just what is an analogue. This court declared that a substance may be a controlled substance analogue only if it satisfies clause (i) and at least one of clauses (ii) or (iii).

There is a fascinating, and potentially most disruptive, appeals ruling made in 1996 concerning the interpretation of this law, in this case involving aminorex and phenethylamine as being analogues of 4-methyl aminorex and methamphetamine, respectively, and thus chargeable as a crime under this analogue statute. This is from the United States District Court for the District of Minnesota, No. 95-2132. In this ruling the Analogue Drug Bill is paraphrased with the following text: "... a drug becomes a controlled substance if it has a chemical structure substantially similar to that of a controlled substance, and either has a substantially similar effect on the user's central nervous system, or a relevant someone represents that it has or intends it to have such an effect." This is fascinating in that the source cited for this quote, 21 U.S.C. SS 802(32)(A), has no such text. And it is potentially disruptive for two reasons. It suggests that an analogue shall become a controlled substance, rather than be treated as if it were a controlled substance. It also introduces a new and undefined term, a "relevant someone." I do not have the legal background to guess the extent that this statement can influence future court challenges in the area of controlled substances analogues. Do, always, keep in mind that the finding that a chemical, in a given situation, is a controlled substance analogue does not make that chemical a controlled substance. The analogue status exists for just the single instance, and the next time the arguments all start over again.

Back to the case involving α-ET. The DEA retreated, licking its wounds, and got its own back by immediately proposing the placement of α-ET into Schedule I. They succeeded, and Monase is today no longer an FDA-approved antidepressant but it is, instead, a drug with a high potential for abuse. One of the more unexpected forms of abuse can be seen in the costs to the researcher who wished to study it in some legal way. Before it became a scheduled drug, alpha-ethyltryptamine was what is known as a "fine chemical" and was listed in the catalog of a major chemical company (1993) for a modest $60.90 for a hundred grams. It became a Schedule I drug by emergency scheduling that same year. Recently (1995) I noted that the chemical has been discontinued (as a fine chemical) but has appeared in a catalog from a major supply house for neurological chemicals. Alpha-ethyl tryptamine now requires a DEA license for purchase, and retailed at $424.00 for 100 milligrams. That calculates out at $424,000.00 for a hundred grams, a price inflation of a factor of almost 7000, or a 700,000% increase. Now THAT is truly drug abuse.

#12. ETH-LAD; 6-NORLYSERGIC ACID, 6-N,N-TRIETHYLAMIDE; 6-NORLYSERGAMIDE, 6,N,N-TRIETHYL; 6,N,N-TRIETHYLNOR-LYSERGAMIDE; N-(6)-ETHYLNORLYSERGIC ACID, N,N-DIETHYL-AMIDE; 9,10-DIDEHYDRO-6,N,N-TRIETHYLERGOLINE-8β-CARBOXAMIDE; N-ETHYL-NOR-LSD

SYNTHESIS: A solution of 0.323 g of lysergic acid diethylamide (LSD) in 10 mL $CHCl_3$ was diluted with 70 mL CCl_4 and added over the course of 1 h to a refluxing solution of 0.44 g BrCN in 30 mL CCl_4 in a nitrogen environment and protected from direct illumination. After the addition was complete, the reaction was held at reflux for an additional 6 h, allowed to cool, and washed with an aqueous solution of tartaric acid. The organic solvents were removed under vacuum, and the residue dissolved in 70 mL CH_2Cl_2 and washed with 50 mL additional tartaric acid solution. The CH_2Cl_2 phase was dried with anhydrous Na_2SO_4, and after removal of the drying agent by filtration, the solvent was removed under vacuum. The residue was cleaned up by passage through 5 g of neutral alumina being eluted with a 9:1 CH_2Cl_2 /MeOH mixture. Centrifugal chromatography with alumina and CH_2Cl_2, under a nitrogen atmosphere containing ammonia, provided a solid product. After recrystallization from IPA or EtOAc, there was obtained 0.24 g (71%) 6-cyano-nor-LSD (9,10-didehydro-N,N-diethyl-6-cyanoergoline-8β-carboxamide) with a mp of 190-191 °C.



To a solution of 0.33 g 6-cyano-nor-LSD in a mixture of 3 mL acetic acid and 0.6 mL H_2O, under a nitrogen atmosphere, there was added 0.6 g powdered zinc and the stirred mixture was heated for 4 h with an external oil bath maintained at 130 °C. The reaction mixture was cooled to ice-bath temperature, diluted with an additional 3 mL H_2O, and brought to an alkaline pH with the addition of concentrated NH_4OH. This suspension was extracted with CH_2Cl_2 (5x10 mL), the pooled extracts dried with anhydrous Na_2SO_4, and the solvent removed (after filtration) under vacuum providing a tan solid. Centrifugal chromatography (with alumina and a 9:1 $CHCl_3$/MeOH elution solvent under an ammonia vapor environment), followed by the removal of the solvent under vacuum, yielded a solid product which was recrystallized from EtOAc/hexanes. There was thus obtained 0.19 g (61%) of tan crystals of nor-LSD (9,10-didehydro-N,N-diethylergoline-8β-carboxamide) with a mp of 196-198 °C (dec.).

To a solution of 66 mg nor-LSD in 2 mL freshly distilled DMF under a nitrogen atmosphere, there was added 48 mg anhydrous K_2CO_3 and 38 mg ethyl iodide. When TLC analysis indicated that the nor-LSD had been consumed (4 h) all volatiles were removed under a hard vacuum. The residue was solubilized in

$CHCl_3$ (5x5 mL) and the pooled extracts dried over anhydrous Na_2SO_4, cleared by filtration, and the solvent removed under vacuum. The residue was separated into two components by centrifugal chromatography (alumina, CH_2Cl_2, nitrogen and ammonia atmosphere) the first of which was the major product. After removal of the solvent, this was dissolved in hot benzene, filtered and cooled. The addition of hexane prompted crystallization of N-ethyl-nor-LSD (9,10-didehydro-N,N,6-triethylergoline-8β-carboxamide) as a white crystalline product weighing 66 mg (61%) after drying. It had a mp of 108-110 °C and an [α]D + 40.5 (c 0.46, EtOH).

DOSAGE: 40 to 150 micrograms, orally

DURATION: 8 - 12 h

QUALITATIVE COMMENTS: (with 20 µgs, orally) "This has a very real effect at this level, whereas I have no response at all from LSD at 20 mikes."

(with 50 µgs, orally) "This is already coming on in fifteen minutes, and is completely developed in another hour. Very few visual changes or distortions but easy eyes-closed imagery. Pretty much out after ten hours; it was a good, repeatable experiment."

(with 60 µgs, orally) "In about an hour or so, gentle movements of the house plants were noted. The painting of the walkway above the fireplace changed as if the sunny spots were moving ahead. The visual aspects became more LSD-like after a couple more hours, though in a very gentle way. The spider windowpane looked three-dimensional: at first I thought the windows were double-paned, but they were not. Stones, rocks and glass had a magical look to them, but tree bark looked like tree bark. Occasionally, a dark streak (spot) would go through the visual field and a page of a book would move sharply without effort. These aspects were very pleasant to me."

(with 75 µgs, orally) "I am up to a ++ within the hour and am feeling lazy. It is very diuretic and certainly not anorexic. Have been dieting strenuously for the past 4 days, but could definitely be interested in food. Also a decongestant. Body feels balanced. Thinking easy. Concepts easy to follow through. Mind and feelings together as should be. Definitely a plus two, no further. I wonder if it would be possible, at any level, to attain that blurring of boundaries that is the plus three at its best? My mind was at all times capable of realistic and down-to-earth thought, this is not a material that will allow you to float two inches off of the floor."

(with 100 µgs, orally) "It sort of sneaks up on you. Certainly not the push of LSD and, sadly, not the sparkle either. Possible time slowing. Easy sleep and no price to pay the next day."

(with 150 µgs, orally) "Extraordinary experience, none of the demands of LSD, just a completely together trip. There were hints of tummy discomfort and some chills early in the trial, but they were trivial and quickly passed. Fine music, and fine sex."

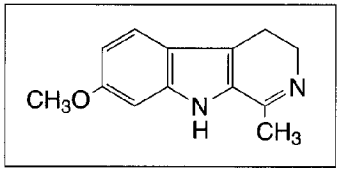
EXTENSIONS AND COMMENTARY: What a remarkable compound. It is a little more potent than LSD, but much less aggressive in the nature of its action. There appears to be little if any of the push, the taking control nature, of LSD and a greatly modified degree of visual distortion. The warmth and humor appears to be there, but all seems more allowing rather than demanding.

I suspect that this material is rather unstable in solution, even as the tartrate in dilute saline, although I cannot guess why that should be. A few months in the dark, at zero degrees and in the absence of air, led to a very real drop in potency, measured by a control assay of a freshly made solution of the same nominal concentration.

What a difference a single atom makes, an ethyl rather than a methyl group at the ring-D nitrogen atom. The absence of any group there (a hydrogen atom rather than the methyl group of LSD or the ethyl group of ETH-LAD) is nor-LSD, the synthetic intermediate mentioned in the preparation recipe above. It has no activity at all, even at a half a milligram. The allyl group at this location gives AL-LAD and the propyl group is PRO-LAD, and both of these are active and have their own individual entries.

#13. HARMALINE; β-CARBOLINE, 3,4-DIHYDRO-7-METHOXY-1-METHYL; 3,4-DIHYDRO-7-METHOXY-1-METHYL-β-CARBOLINE; 3,4-DIHYDROHARMINE; 7-METHOXYHARMALAN; HARMADINE

SYNTHESIS: To a solution of 0.033 g 6-methoxytryptamine in 3.5 mL 0.1 N HCl, there was added 0.011 g glycolaldehyde and the mixture was heated on the steam bath for 1.5 h. The solution was then made basic with 10 mL 0.5 N NaOH, and extracted with Et_2O on a continuous extractor. The Et_2O extracts were pooled, dried over solid KOH, the solvent removed under vacuum. The residue was an oil that crystallized to give a solid, mp 170-175 °C, presumably a hydrate of 1-hydroxymethyl-7-methoxy-1,2,3,4-tetrahydro-β-carboline.



This was treated with 2.5 mL 90% H_3PO_4 and heated on the steam bath for 2 h. After dilution with H_2O, this was made alkaline with aqueous NaOH and extracted with Et_2O. The pooled extracts were stripped of solvent under vacuum, and the residue distilled to give a fraction (bp 120-140 at 0.001 mm/Hg) that weighed 0.027 g (72%). MS (in m/z): Parent ion -1, parent ion, 213, 214 (100%, 89%); 198 (29%); 201 (23%); 170 (22%); 173 (19%). IR (in cm^{-1}): 817, 832, 916, 1037, 1139, 1172. Harmaline hydrochloride dihydrate; IR (in cm^{-1}): 820, 841, 992, 1022, 1073, 1137.

There is a little bit of interesting history connected with the melting point of harmaline. A report appeared that described an alkaloid from *Peganum harmala* that looked like harmaline but which melted 18 °C too high, and so it was thought to be an isomer and was given the name harmadine. This was all cleared up a few years later when it was observed that on an open melting point block, harmaline had a mp 242-244 °C (with beginnings of sublimation at 189 °C) and harmadine had the values of 241-243 °C and 178 °C. In a capillary tube, harmaline melted at 256°C and harmadine at 257 °C. So, harmadine is now a synonym for harmaline.

DOSAGE: 150 - 300 mg, orally

DURATION: 5 - 8 h

QUALITATIVE COMMENTS: (with 100 mg, orally) "I have tried this on two occasions, essentially without effect."

(with 150 mg, orally) "In an hour and a quarter, there was a rapid-onset intoxication and I felt a little unstable. And a little bit numb. There was an unusual shimmering in my lateral vision when I turned my head to the side. Everything was just a little bit down. Music was pretty much normal but I was missing the higher frequencies. Even light food sat heavily, and I wasn't too hungry (and I was remembering to watch what I eat, with this monoamineoxidase stuff). Sex was difficult — probably due to some reduced sensations. I feel that this compound is unlikely to be attractive to most people, as its major effects are an intoxication with a clouding of thoughts and some disruption of musical relationships."

(with 175 mg, orally) "After about one hour I found myself becoming relaxed and a bit sloppy. By the end of the second hour, I had peaked, and was pretty much at baseline after five hours. At the peak, three areas of disturbance were obvious. There were obvious tracers — when looking at a bright object, and moving your eyes to the side, the image of the object lags in its leaving the visual field, and it leaves in the opposite direction. As to the auditory, it seemed as if the higher frequencies of music were attenuated, and the lower frequencies amplified. And as to touch, there is a definite numbing. I had no appetite, and the little I ate didn't taste particularly good."

(with 200 mg, orally) "At about the two hour point I remember three things. The first was the effort to bring into reality the visual image of a face that was playing with my eyes-closed imagery. I got the mouth and, after a bit of work, I got the eyes. So I concentrated on the nose and it came into view, finally, but it was upside down. The second and third things were more easily defined. Nausea and diarrhea. Fortunately they alternated. This is not my trip of choice."

(with 300 mg, orally) "I was in a psychotherapy environment, so there were some suggestions and leading that influenced my responses. But I have great difficulty reliving my experience, in fact I don't remember anything. I have only disconnected images. There is a girl — me — in front of a church on a dusty road, myself at communion, receiving the Host from an invisible hand at a grandiose altar. I feel that I am going crazy. Something inside. It is not anxiety. It is not depression.

It is some of each, plus irritation and disorientation. I am dead but still have to come back to life. I am facing a reality of mine that I cannot accept."

(with 400 mg, orally) "This is Fluka material, and has a nasty taste. I felt completely immobilized and sick to my stomach. Closed eyed visuals yielded native women, 'organic' colors and shapes, and a black panther! I would like to do DMT and Harmaline together, but am put off by the nausea."

(with 500 mg, orally) "I took a half gram of pure synthetic harmaline after fasting for over a day. The resulting nausea was greatly attenuated after I vomited. At this dose there were intense and annoying visual disturbances, and complete collapse of motor coordination. I could barely stagger to the bathroom, and for safety's sake locomoted by crawling. Tracers and weird visual ripplings disturbed my sight with open eyes. With eyes closed, there was eidetic imagery. It had no symbolic significance, just bothersome disjointed sequences that lacked a relevant theme. They proceeded to transform so slowly (in comparison to the speed of my thought) that they were predictable and boring. Throughout the experience I just lay hoping it would end soon. It did not seem as though I had encountered intrapsychic material which was being expressed through somatic symptoms. Rather, I felt that I was struggling to metabolize a chemical disruption of my physiological functions. Although the session was not enjoyable, I was satisfied at having educated myself about the effect produced by a penalty dose of this compound."

(with 2 g *Peganum harmala* seeds, ground, in capsules) "No effects."

(with 5 g *Peganum harmala* seeds, ground, in capsules) "At about 1:45 tinnitus was obvious. At 2:00 precise movements were problematical and nystagmus was noticeable. Mild nausea and diarrhea, but no vomiting. I was sensitive to light and sound, and retired to a dark room. Hallucinations were intense, but only with the eyes closed. They consisted, initially, of a wide variety of geometrical patterns in dark colors, getting more intense as time went on. They disappeared when the eyes were opened. Although the loose bowels and nausea were pretty constant through the first part of the trip, I was not afraid. It was as if the "fear circuits" in the brain had been turned off. The geometric shapes evolved into more concrete images, people's faces, movies of all sorts playing at high speed, and animal presences such as snakes. It was like vivid and intense dreaming except that I remembered most of it afterwards. In another hour things became manageable and I could go out in public. My sex drive was pleasantly enhanced, and I slept very well."

(with 7 g *Peganum harmala* seeds, ground, in capsules) "Very sick for 24 hours."

(with 20 g *Peganum harmala* seeds, as extract) "This is equivalent, probably, to a gram or so of the harmala alkaloids. This was ground up material extracted with hot dilute lemon juice. Within a half hour, I found myself both trippy and sleepy. Then I became quite disorientated, nauseous, and with an accelerated heart beat. I had the strong sensation of moving backwards, drifting, with faint visuals under my eyelids. Restraining the vomiting urge was an ongoing problem.

I could have gone out of body quite easily, except that I was completely anchored by the nausea. After about three hours, I knew that it had peaked, and I went to sleep and experienced intense and strange dreams. The entire experience was a conflict between tripping and being sick. I want to explore this more."

(with 28 g *Peganum harmala* seeds, as extract) "I sat up late one night drinking gulp after gulp of tea from about an oz. of seeds, periodically adding more water and simmering. This process took several hours, and though I had read up on harmaline, I didn't know quite what to expect. Suddenly it hit me like a wall. It was starting to get light outside and as I shifted my gaze, zebra-like stripes of light and dark spiraled off the perimeter of the window silhouettes. Every time I shifted my focus my visual field would shudder and swirl before settling down. This visual effect had a physicality unlike those of any other entheogen I'd experienced. Rather than patterns revealing greater order in sensation, these were waves of chaos revealing no particular order and urging the mind to retreat from the disturbing realm of sensation. Accompanying this was a pronounced auditory buzz. Lying down and closing my eyes I left the physical symptoms behind and explored the vivid spontaneous imaginations evoked by this state. Unfortunately, it was getting light, which made it harder to shut out the distracting world of sensation. I resolved to conduct future sessions in the night-time (and always in a quiet, undisturbed place).

"A second trial was made at the same level. This time it came on very fast. That tremendous buzz on the other side of which are the wondrous realms of the subconscious. The most memorable impressions from this trip were of weird animals. I imagined myself spinning on a merry-go-round of strange winged creatures. I started to feel very sick and negotiated my way to the bathroom to face the inevitable — voiding from both orifices simultaneously. It proved cathartic, and released me to experience the state more fully. I remember traveling to jungle-like places, full of imagery of vines, fountains, and animals. Minutes seemed like hours as I roamed in these spaces. Though the sensory effects were very disturbing when I got up, given the high dose level, I could easily ignore my body when laying down and traveling in my mind."

EXTENSIONS AND COMMENTARY: Right off the bat, I must make an apology, in that I have commingled reports employing harmaline as a single chemical, with reports employing seeds from *Peganum harmala*. This is, of course, pharmacological nonsense in that harmaline is a pure chemical substance, whereas the seeds of the *P. harmala* contain harmine as well, along with a lot of other alkaloids that could well play some role in its psychopharmacology profile.

There is a valid reason for this commingling of the reports of the effects of this chemical and plant, however. In many people's minds, the two materials are felt to be exclusively monoamineoxidase inhibitors, and to be interchangeable. I recently read the following bit of advice somewhere on the internet. "If you really want to get off on 'shrooms, take some harmaline or Syrian Rue seeds along with

them." This one phrase embodies a number of popular myths in the psychedelic drug subculture. Let me try to unravel this tangled knot.

Some drugs are metabolized by the removal of the needed amine function. This deamination results from the action of an enzyme system that is called a monoamineoxidase, or a MAO. If this enzyme system is inhibited, then the drug would be destroyed to a lesser extent, and would have a greater potency. The material that protects the drug from this erosion is called a monoamineoxidase inhibitor, or a MAOI. As a result, some drugs that do not show any oral activity (such as DMT) become available when the oxidizing enzymes are made dysfunctional by an inhibitor. This is the heart of the chapter Hoasca vs. Ayahuasca, where this argument is treated at length. But, there is a general inference that the MAOI is, itself, without action and this is simply not correct. They might show some activity in that there are a lot of dietary amines, some of them pretty toxic things, that normally do not bother us since our body defenses can destroy them. Take away that defense, and they can express their toxicity. But I truly believe that there can be a complex spectrum of pharmacological properties that are intrinsic to the inhibiting drug. A goodly number of our prescription anti-depressants on the market today have exactly this mechanism of action.

That is the reason for the presentation of the effects of harmaline by itself, and of *Peganum harmala* seeds, just by themselves. They are very different from oneanother, although both can be pretty rough on the body.

Now, I would like to reenter the qualitative comments mode, this time with the use of harmaline or *Peganum harmala* in conjunction with a second drug. In some of these examples, the inhibitor was taken ahead of the actual tryptamine, as indicated by the time statement.

FURTHER QUALITATIVE COMMENTS:

WITH DMT

(with 20 mg harmaline and 55 mg DMT) "There was nothing for three hours, and then I became aware of some eyes-closed hypnogogic abstractions. The peak was slightly longer with adrenergic push somewhat more intense than what the mild psychic effects would suggest. The come-down was equally drawn out. It all was certainly less intense than when the DMT is smoked."

(with 50 mg harmaline, 60 mg DMT [20 min]) "No effects were noted except for perhaps a brief suggestion of some increase in motor activity."

(with 80 mg harmaline, 40 mg DMT [60 min]) "There was quite a bit of visual activity. The onset was subtle, but the drop-off was quick."

(with 100 mg harmaline, 120 mg DMT [10 min]) "It was not until 80 minutes into the experiment that it became clear that CNS effects were occurring. Initially this was felt as clarity of detail of everything around me followed by slight time distortion. There was no loss of reality but closed eye imagery developed rapidly, later becoming present even with eyes open, even though less intense. Images were initially very colorful, consisting of sheets of patterns infinitely repeated with some gentle waviness, somewhat like looking through a kaleidoscope. Deliberate shifting of attention was possible at all times and although gait was mildly affected it was possible to perform any given task with concentration. There was no loss of identity or reality. Pupillary movements did not change the area of focus of my 'sight,' which was surprising. Images could be willfully dismissed as desired with eyes open. Music became another world with headphones on, and 'Hearts of Space' albums easily became voyages which could be interrupted at any desired point with eyes opening. The effects began to recede at the two and a half hour point. The bright colors and patterns had shifted to less intense scenery in a calm, peaceful way. At no time was there any noticeable amphetamine jaw-clenching, hyperactivity, or restlessness. The entire episode had ended at the four hour point leaving an intense feeling of happiness and amazement. Sleep was easy at five hours, and yet for the subsequent 30 hours my concentration was noticeably impaired. There were no motor problems or incoordination, yet short-term memory was significantly disrupted, requiring deliberate concentration on minor things. At 38 hours my mental condition seemed back to normal. The only criticism I might make of this experience was that there seemed to be none of the insight that I had experienced with TMA-2. This seems, however, to be a very psychologically safe experience for almost anyone and was very enjoyable."

(with 150 mg harmaline, 35 mg DMT [20 minutes]) "Initial effects were noted at 70 minutes, characterized by feelings of mild intoxication followed by significant visual distortions and inability to focus thoughts. By two hours, colored patterning was present with eyesclosed, but the images flashed through consciousness so quickly that they could not be considered or analyzed. There was a pronounced sensation of being cold that was difficult to change, despite a very warm heating blanket. An interesting finding was that I was unable to visually "picture" some desired scene. In other words, I could verbally say that I wanted to visualize a forest, or a horse, or a tree, but none of these items could be brought forward. The rapid flood of thoughts quickly became exhausting and there was a strong desire to avoid all stimuli, including music, TV, or any other sounds. The effects began declining at the three-hour point and were essentially gone at five hours. I am beginning to reach the conclusion that DMT has few redeeming qualities. So far, it cannot compare with the insight and clarity of thought which occur with some of the phenethylamines and phenylisopropylamines. This potent activity at the 35 milligram level suggests that the 150 milligrams harmaline dose is highly effective as an MAO blocker."

(with 150 mg harmaline, 80 mg DMT [20 min]) "At just about an hour into it there was a rapid onset intoxication with some staggers and difficult walking. During the next half hour, there were closed-eye visuals along with nausea and a severe depression. I turned on all the lights in the room for security, although I do not like bright lights. I considered calling a friend on the phone, but then I realized

that nothing could reassure me at this point. Intellectually I knew that I was safe, but psychologically there was overwhelming loss of self worth and a feeling of despair. This was a severe ego-smashing experience which might have been diagnosed as psychosis if a psychiatrist had been present. The effects lasted longer than anticipated, with a gradual return to normality at the fifth hour, and an hour later I slept. Despite the negative experience, the next day I realized that I had viewed many aspects of my life with extraordinary clarity and insight, and as a result of this experience I intend to try to change several of these personal flaws."

(with the extract of 3 g *Peganum harmala* seeds, 40 mg DMT) "The DMT was noticeably effective just over an hour following ingestion, and it built up to a peak rather quickly. It stayed there for an hour, then dropped off. I would call the overall effect mild."

(with the extract of 5 g *Peganum harmala* seeds, 20 mg DMT [0 min]) "There was a feeling of aliveness and excitement, above and beyond the effects of this amount of harmel seeds alone."

WITH 5-MeO-DMT

(with 70 mg harmaline, 10 mg 5-MeO-DMT [0 min]). "I felt changes in pressure around the eyes at 18 minutes, and there was a floating feeling when walking. I had peaked at an hour and a half, probably at a plus three, with no visuals, no emotionals, no intellectuals, no negative, no positive. A little nausea. I am not sure why I am at a +++ but I am. By the 2 hour point I am coming down. At three hours, I noticed a complete change of character, the harmaline was beginning to kick in. This grew in intensity for several hours, with quite a bit of nausea. This was fully equivalent to 300 mg. harmaline alone, but without the physiological noise. At 12 hours I got a little sleep with a lot of dreams."

(with 80 mg harmaline, 10 mg 5-MeO-DMT) "This was conceptually very active. Extremely rewarding. Remarkable difference from the harmaline alone, or the tryptamine alone, neither of which would have been active taken this way, orally."

(with 150 mg harmaline, 25 mg 5-MeO-DMT [60 min]) "In about 15 minutes I began to feel the typical effects of 5-MeO-DMT, a gradually building emotion of solid, somewhat boiling, turbulent feeling. I began to feel like vomiting so I did so, several times. Waves of the inner feeling would approach, completely removing my awareness of the physical world, but it never reached that point as it does when I have smoked 12 milligrams of 5-MeO-DMT alone. The experience was quite intense but I never felt a great deal of fear. I consciously debated whether or not to smoke some 5-MeO-DMT in order to break through this 'middle' level of experience into a complete transcendent state as I had experienced in the past. But the complexities of asking for the pipe and managing to smoke it seemed too much, even with assistance. I abandoned the idea.

"I started to come 'down' into a more differentiated consciousness, and the

first thing I felt was a powerful, aggressive sexual feeling. I was not wearing any clothes and I spent a long time, over an hour, writhing around, occasionally uttering phrases of one or three or four words of a very hostile and/or sexual nature. I remember saying I hated my sitter (a female) and God, but it was quite clear that it was the sexual/maternal image of the sitter that I hated as something that I desired and felt dependent upon while resenting that I needed something I did not have within myself. The next phase found me physically calm and quiet. Finally, after four hours, I felt sleepy and comfortable. I ate well, and was in a good mood.

"I do not feel that taking a higher dose orally would necessarily have pushed me through to the state achieved by smoking because the onset was so, so slow. I don't think I'll repeat this combination."

WITH TMPEA

(with 150 mg harmaline, 200 mg TMPEA (2,4,5-trimethoxy-phenethyl-amine) [20 min]) "A very faint peripheral visual flicker was noted at 40 minutes. By 80 minutes, a decrease in coordination was apparent and walking required somewhat more attention than normal. This incoordination increased gradually, peaking at three hours. By this time the visual latency characteristic of harmaline was pronounced (when rotating the head or gazing quickly in a different direction, the prior images exit the visual field in a multiple wave fashion in a direction opposite to the motion). At no time were there any detectable effects on thought, and there was no open- or closed-eye imagery, with or without music. No effects were detectable at the five hour point and sleep was easily achieved shortly thereafter. In summary, there was nothing there that could not be explained by the harmaline alone."

WITH MESCALINE

(with 100 mg harmaline, 60 mg mescaline (3,4,5-trimethoxy-phenethyl-amine) [20 min]) "At two hours I was in a pleasant state of physical relaxation, a fine sense of well being, and I found music most enjoyable. From then to the fourth hour, thoughts flowed freely, and it became obvious that insight was a major part of this experience. Normally unconscious thoughts were easily available. It was as if I could observe my mind in operation, as facts were weighed to form conclusions. By the sixth hour music was a thing of beauty, with the higher notes crisp and clear. The harmaline has probably worn off. Sleep at eight hours, and the next day was without any adverse effects. This was a remarkable experience, the insight of TMA, and the relaxation of MDMA."

(with 150 mg harmaline, 100 mg mescaline [15 min]) "A stomach ache developed at about 45 minutes, followed by a mild nausea which occurred intermittently throughout the next six hours. I felt comfortable, although there was a slight discoordination at about two hours. Walking was never a problem but did

it flat with your finger? The dictionary says that a teaspoonful contains exactly 1.333 fluid drams. Indeed! Let's look it up. You will discover that this is a total cop-out if you read the dictionary definitions of dram: (1) 1.771 grams if you are using the avoirdupois system, or (2) 3.887 grams if you are using the apothecaries system. So, how does a non-pharmacist person, without an analytical scale or an immediate command of the avoirdupois versus apothecaries vocabulary, measure a wanted quantity of *Peganum* seeds?

I would suggest using the following scale, remembering that, with water, weights can be easily interchanged with volumes, since water has a weight that is equal to its volume. In both of these scales, the water and the rue, the teaspoon is the small semi-spherical thing in the cork-puller drawer, leveled off:

—— This is for water ——

1 teaspoon water =				0.16 ounces (5 grams)
3 teaspoons =	1 tablespoon =			0.5 ounce (14 grams)
	2 tablespoons =			1 ounce (28 grams)
	4 tablespoons =	1/4 cup =		2 ounces
	16 tablespoons =	1 cup =	1/2 pint =	8 ounces
		2 cups =	1 pint =	1 pound
			2 pints =	1 quart
				4 quarts = 1 gallon

or, as I had learned as a childhood rhyme: a pint's a pound, the world around.

You must remember, this volume thing has its own traps. When you start using the volume measurement for things such as seeds, or bark, or leaves, or other biological things that are not of the density of water, they possess varying degrees of fluffiness, and the weights will be less than the volumes. The Rosetta stone translation that is appropriate here is based on the fact that the *Peganum harmala* seeds are just over half the density of water. And, since they may contain from 2 to 6% their weight in alkaloids, the following equations are useful:

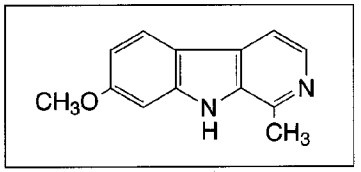
—— This is for the seeds of Syrian rue ——

1 teaspoon rue seeds =	3 grams =	60-180 mg alkaloids
1 tablespoon rue seeds =	9 grams =	200-600 g alkaloids
1 large (OO) gelatin capsule with ground rue seeds =	0.7 gram =	15-45 mg alkaloids

But do remember, with the harmaline and harmine content of the seeds of *Peganum harmala*, you are also accepting an equal weight of quinazoline alkaloids with pharmacological properties that are quite different from those of the carbolines.

#14. HARMINE; β-CARBOLINE, 7-METHOXY; 7-METHOXY-β-CARBOLINE; BANISTERINE; YAGEINE; TELEPATHINE; LEUCOHARMINE

SYNTHESIS: To a solution of 0.5 g harmaline hydrochloride dihydrate in 8 mL EtOH containing 8 mL concentrated HCl there was added a solution of 0.25 mL concentrated HNO_3 in 7 mL EtOH. This was heated on the steam bath until an exothermic reaction set in, with considerable bubbling. Heating was continued for 0.5 min, and then the reaction mixture was cooled, producing a crop of fine crystals, which were removed by filtration and washed lightly with EtOH. With air drying, there was thus obtained 0.31 g (67%) harmine hydrochloride monohydrate which was dissolved in 3.1 mL H_2O and neutralized with a few drops of concentrated NH_4OH. There separated a fine, pale cream solid that was removed by filtration and air dried, to give 0.22 g (89%) harmine base as an off-white powder. MS (in m/z): parent ion 212 (100%); 169 (67%); 197 (24%). IR (in cm^{-1}): 819, 951, 1037, 1110, 1138, 1165. Harmine hydrochloride hydrate, IR (in cm^{-1}): 737, 800, 821, 1021, 1076, 1110, 1138, 1162.



DOSAGE: unknown

DURATION: unknown

QUALITATIVE COMMENTS: (some reports paraphrased from literature summations)

(with 25-75 mg, s.c.) L. Lewin found this to produce euphoria which Turner et al. insisted should not be regarded as a hallucinogenic reaction.

(with 35 mg, orally, and separately intranasally) "In neither occasion was a notable psychoactive or somatic effect felt, and harmine could not be detected in any of the plasma samples."

(with 35-40 mg, i.v.) "The most frequent symptoms were bradychardia, trouble in focusing the eyes, tingling, hypotension, cold extremities and lightheadedness. All symptoms disappeared within 45 minutes after the injection except bradychardia in two subjects and drowsiness in three subjects."

(with 40 mg, orally) "There was an immediate sensation of excitement with difficulty remaining in one place. Restlessness was the predominant symptom. All activity was performed as if with greater ease, and no clouding of the senses was described. It appeared to be a consequence of 'central cortico-motorstimulation.' I felt as if consciousness was packed with ether. When lying on a sofa, the lightness increased to a feeling of a fleeting sensation, and the weight of the body was subjectively less."

(with >40 mg, orally) "The excitement I felt was increased even in a belligerent way. Although it is not my nature, I started a fight with a man in the street where I was the one who attacked. Even though, according to the circumstances, the prospect for me was unfavorable."

(with 140 mg, orally) "There was no stimulation, no suggestion of entheogenic response, perhaps a little bit of sedation which was still evident several hours later. It was sufficiently mild as to make me forget I had ingested anything."

(with 150-300 mg, i.v. [clinical distillation of Pennes and Hoch]) "With this route, 5 of 11 subjects reported visual hallucinations of varying degrees of complexity and organization. Bradycardia and hypotension occurred with all doses of intravenous harmine despite a 20 to 30 minute injection time, thereby limiting maximum dosage to 300 mg. Recovery occurred in about 30 minutes. The drug was hallucinogenic by oral or subcutaneous routes."

(with 300 mg, sublingually) "I found myself pleasantly relaxed and withdrawn from my environment. There was a slightly diminished capacity to concentrate."

(with 300-400 mg, orally [undocumented claim by Clarke]) "Produces psychotic symptoms."

(with 750 mg, sublingually) "Dizziness, nausea and ataxia were the neurological symptoms observed. I do not choose to go any higher — there must be other substances that are responsible for the hallucinogenic effects of Ayahuasca."

(with up to 900 mg, orally [clinical distillation of Pennes and Hoch]) "Visual hallucinations might have occurred."

EXTENSIONS AND COMMENTARY: Here I am being just a bit nasty. What a hodge-podge of published reports which are, in several cases, simply quoted here from the literature. Up the nose, down the throat, under the tongue, in the arm. Claims of irrational aggression at about 30 milligrams can be contrasted with claims of virtually nothing happening at all at up to a gram. I have no choice but to give the dosage as "unknown" and to let the reader pick and choose what fits his fancy. One of the most dramatic syntheses of chemistry with medicine can be found in a viewing of the treatment of the symptoms of Parkinson's Disease. The clinical course of PD had been well characterized by the turn of the century. One of the more bizarre aspects of the syndrome is the alternation of periods of total immobility with those of easy movement. To the extent that these changes might be part of willful action, it was suspected by some physicians that the disease might have psychological components, and be a kind of neurosis. This led to the exploring of a number of psychotropic agents in the search for therapies.

It was Louis Lewin, of *Phantastica* fame, who first suggested that banisterine might be useful in the treatment of diseases of the nervous system. And it was Kurt Beringer, of *der Meskalinrausch* fame, who ran the first clinical study using banisterine on 15 patients with postencephalitic parkinsonism, in 1928. Other studies reinforced the virtues of this drug. Initially, doses of 20 or 40 mg were

administered intramuscularly, and within 15 minutes the patients had less motor rigidity and were able to move more freely. Even when used orally, at 10 mg thrice daily, the responses were remarkable. In some cases the tremor was diminished, and in others it was exaggerated, but in general the mental status of the patients was brightened, without producing "psychic" effects. Banisterine became the wonder drug of the year, the feature stuff of the Sunday Supplements.

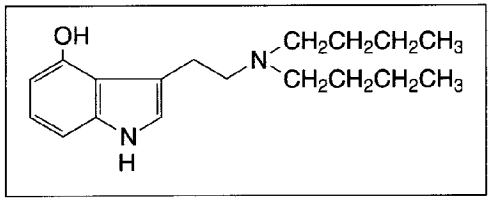
Then, through a series of events, it fell out of favor just as rapidly. A large study involved patients who had been controlled rather well with scopolamine. They were withdrawn from treatment for a week, deteriorated rather badly, and to a large measure failed to respond to banisterine. And at about this time another researcher, a German physician Dr. Halpern, involved herself in self-experimentation (the physician of the 40 and >40 milligram quote above) and published these findings at the time of this excitement. Belligerency is not necessarily a good property for a drug to have in the treatment of sick people. Then it became popularized that banisterine is really an old and well-known plant product called harmine. The pharmaceutical industry was evolving into the preference for synthetic materials that were patentable, and losing interest in natural products that were not patentable. What a short but fascinating bit of medical history.

There is a strange overlap between the chemistry of harmine and that of a botched synthesis of a meperidine analogue. During the illicit synthesis of what was called the reverse ester of meperidine, the propionate esterification of 4-phenyl-4-hydroxy-N-methylpiperidine, dehydration occurred instead, producing a compound called 4-phenyl-N-methyl-1,2,3,6-tetrahydropyridine, or MPTP. This wrong product was injected as if it were meperidine, and produced immediate and irreversible Parkinsonism in the user. What happens in the brain is that the material is aromatized to form a quaternary salt, called MPP+, a toxic metabolite. If a N-methyl bridge were to be put between the two rings of MPP+, one would have a carboline, one that could in theory be produced from harmine. This material, 2,N-dimethylharmine has been synthesized, and vies with MPP+ as a neurotoxin. What is it we can't see, here? Harmine can serve as a treatment for Parkinson's disease, and a dimethylated harmine can be a potential causative agent for Parkinson's disease.

As with harmaline, a number of drug combinations have been studied using harmine as the potential deaminase inhibitor. This is much closer to the basic structure of ayahuasca, where the plant *Banisteriopsis caapi* is the native inhibitory component, and it contains much more harmine than harmaline. In measured experiments, the use of harmine in the 140 to 190 milligram range, administered with 35 to 40 milligrams DMT, produced unmistakable effects lasting from one to three hours. Trials with smaller amounts, with 120 to 140 milligrams of harmine and 30 milligrams of DMT, produced no signs of central activity at all. Harmine apparently is an effective, although modest, promoter of oral activity of DMT. At least this occurs at levels where it itself is substantially without action, so here it may truly be a facilitator rather than a participant.

#15. 4-HO-DBT; TRYPTAMINE, N,N-DIBUTYL-4-HYDROXY; 4-INDOLOL, 3-[2-(DIBUTYLAMINO)ETHYL]; N,N-DIBUTYL-4-HYDROXYTRYPTAMINE; 3-[2-(DIBUTYLAMINO)ETHYL]-4-INDOLOL

SYNTHESIS: A solution of 0.50 g 4-acetoxyindole (see under 4-HO-DET for its preparation) in 5 mL Et_2O was stirred and cooled to 0 °C with protection from atmospheric moisture. There was then added 0.5 mL oxalyl chloride. The reaction mixture was stirred for an additional 30 min, and the intermediate indoleglyoxyl chloride separated as a yellow crystalline solid but was not isolated. This was treated with a 40% solution of dibutyl amine in anhydrous Et_2O, dropwise, until the pH was 8-9. The reaction was diluted with 100 mL $CHCl_3$ and shaken with 30 mL of a 5% aqueous $NaHSO_4$ followed by 30 mL of a saturated aqueous $NaHCO_3$ solution. After drying over anhydrous $MgSO_4$, the organic solvents were removed under vacuum. The residue was recrystallized from cyclohexane/hexane to give 0.78 g (77%) of 4-acetoxy-indol-3-yl-N,N-dibutylglyoxylamide with a mp 123-125 °C. Anal: C,H,N.



To a stirred suspension of 0.50 g LAH in 10 mL anhydrous THF stirred under nitrogen, at room temperature, there was added a solution of 0.75 g 4-acetoxyindol-3-yl-N,N-dibutylglyoxylamide in 10 mL anhydrous THF. This was added dropwise at a rate that maintained the reaction at reflux. When the addition was complete, the reflux was maintained for an additional 15 min and then the reaction was cooled to 40 °C. The excess hydride and the product complex were destroyed by the addition of 1.0 mL EtOAc followed by 3.0 mL H_2O. The solids were removed by filtration, the filter cake washed with THF, the filtrate and washings pooled, and the solvents removed under vacuum. The residue was distilled at the KugelRohr and the distillate recrystallized from EtOAc/hexane. Thus there was obtained 0.19 g (35%) of N,N-dibutyl-4-hydroxy-tryptamine (4-HO-DBT) with a mp 74-75 °C. C,H,N.

DOSAGE: >20 mg, orally

DURATION: unknown

QUALITATIVE COMMENTS: (with 20 mg, orally) "No effect."

EXTENSIONS AND COMMENTARY: This was a total disappointment. With the remarkable activity of the diisopropyl compound (4-HO-DIPT) this seemed to be a promising candidate for activity. Especially interesting would be the di-sec-butyl isomer with the same branching of the chain right at the position of attachment to the basic nitrogen atom.

Allow me a moment to present to the non-chemist a lay definition of what is being talked about here. This is one of the most exciting, and most annoying, tidbits of what could be called isomeric aliphatic chain branching. Please, all non-chemists, forget that I used that phrase. Let me give a simple demonstration of the weird terms (such as methyl, ethyl, propyl, butyl) and prefixes (such as normal, iso, secondary, tertiary) that have been part and parcel of this second half of the book. Let me give you, hypothetically, any number of tennis balls (my metaphor for carbon atoms) from one (initially) to four (at which point I will abandon ship). You are to put them (however many you have) up against the tennis net in every possible way.

You have one tennis ball. There is only one way you can do it. There is the net (the nitrogen atom with an implacable point of attachment, that can touch only one ball at a time, at least in this example), and here is the ball (the carbon atom that has to be attached to it):

N - C one carbon is methyl,
there's only one way it can be attached.

Now you have been given two tennis balls:

N - C - C two carbons is ethyl,
there is only one way you can attach them.

Now you have been given three tennis balls:

N - C - C - C three carbons is propyl,
this is one way they can be attached
(known as propyl).

But a second possibility emerges:

N - C - C
|
C

the third tennis ball can touch the first,
rather than the second ball
(known as isopropyl).

Now you have been given the fourth tennis ball:

N - C - C - C - C four carbon atoms is butyl,
this is one way they can be attached
(known as normal butyl),

```
N - C - C - C      the fourth ball can touch the first,
    |              this is another way they can touch
    C              (known as secondary butyl, or s-butyl),

N - C - C - C      the fourth ball can touch the second,
        |          this is yet another way they can touch
        C          (known as iso butyl, or i-butyl),
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(of course, if the fourth ball touches the third, you have the normal butyl, as shown before)

```
    C              the third and fourth ball can touch the first one,
    |              this is the fourth way they can touch
N - C - C          (known as tertiary butyl, or t-butyl).
    |
    C
```

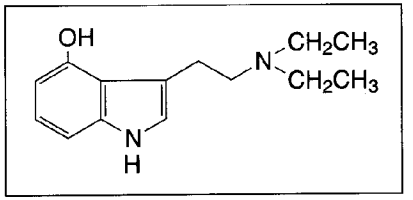
You can have one of the four tennis balls touching two of the others at the same time (as well as touching the nitrogen); this formation is known as a cyclopropyl ring. Four of them all touching one another gives a cyclobutyl ring. You can see that when the number of tennis balls gets into the many dozens, the isomer count gets into the many millions, because there can be not just straight out, but ups and downs as well, and little rings and big rings and multiple rings, and cross-linking and everything and anything that can be imagined. That, in a word, is what makes chemistry fun. When two groups that are the same are both attached to the nitrogen atom, you have a di-compound, and with this four-tennis ball analogy, you can have dibutyl, or di-i-butyl, or di-s-butyl or di-t-butyl tryptamine and, of course, all possible mixtures.

Back to the rational world. Two n-butyl groups gives the compound 4-HO-DBT, the theme of this recipe. It is not active at 20 milligrams, but I suspect that it will be so at a somewhat higher dose. There is the secondary-isomer, 4-hydroxy-N,N-di-s-butyltryptamine (4-HO-DSBT, an oil that never crystallized) which should be an isomer of increased activity, but it has not been assayed. The iso-isomer (4-HO-DIBT, mp 152-154 °C) should be yet less active as the steric mess around that important nitrogen atom is much larger, and indeed it is not active at the same 20 milligram level. The tertiary isomer (4-HO-DTBT) has yet to be made and, as it is extremely crowded around that innocent nitrogen atom, it may be unmakable. The activity is unknown, as the compound itself is unknown. The four methyl butyl possibilities are all known, and are mentioned in the recipe for 4-HO-MPT.

#16. 4-HO-DET; TRYPTAMINE, N,N-DIETHYL-4-HYDROXY; 4-INDOLOL,3-[2-(DIETHYLAMINO)ETHYL]; N,N-DIETHYL-4-HYDROXYTRYPTAMINE; 3-[2-(DIETHYLAMINO)ETHYL]-4-INDOLOL; CZ-74

4-HO-DET PHOSPHATE ESTER; TRYPTAMINE, N,N-DIETHYL-4-PHOSPHORYLOXY; 4-INDOLOL, 3-[2-(DIETHYLAMINO)ETHYL], PHOSPHATE ESTER; N,N-DIETHYL-4-PHOSPHORYLOXYTRYPTAMINE; 3-[2-(DIETHYLAMINO)ETHYL]-4-INDOLOL, PHOSPHATE ESTER; CEY-19

SYNTHESIS: To a solution of 5.0 g 4-hydroxyindole in 20 mL pyridine there was added 10 mL acetic anhydride and the reaction heated on the steam bath for 10 min. The reaction was quenched by pouring over chipped ice to which was added an excess of $NaHCO_3$. After being stirred for 0.5 h the product was extracted with EtOAc and the extracts washed with brine and the solvent removed under vacuum. The residue weighed 6.3 g (95%) which, after crystallization from cyclohexane, had a melting point of 98-100 °C. IR (in cm^{-1}): 1750 for the carbonyl absorbtion.



To a solution of 0.50 g 4-acetoxyindole in 4 mL Et_2O, that was stirred and cooled with an external ice bath, there was added, dropwise, a solution of 0.5 mL oxalyl chloride in 3 mL anhydrous Et_2O. Stirring was continued for 0.5 h and the intermediate indoleglyoxylchloride separated as a yellow crystalline solid but it was not isolated. There was then added, dropwise, a 40% solution of diethylamine in Et_2O until the pH was raised to 8-9. The reaction was then quenched by the addition of 100 mL $CHCl_3$, and the organic phase was washed with 30 mL of 5% $NaHSO_4$ solution, with 30 mL of saturated $NaHCO_3$, and finally with 30 mL of saturated brine. After drying with anhydrous $MgSO_4$, the solvent was removed under vacuum. The residue set up as crystals and, after recrystallization from Et_2O, provided 0.62 g (72%) 4-acetoxyindol-3-yl-N,N-diethylglyoxylamide with a mp of 150-151 °C.

A suspension of 0.5 g LAH in 10 mL anhydrous THF was held in an inert atmosphere and vigorously stirred. To this there was added, dropwise, a solution of 0.6 g of 4-acetoxyindol-3-yl-N,N-diethylglyoxylamide in 10 mL anhydrous THF at a rate that maintained a gentle reflux. After the addition was complete, the refluxing was maintained for an additional 15 min, cooled to 40 °C, and the excess hydride killed by the addition of 1.0 mL EtOAc, followed by 2.3 mL H_2O. The reaction mixture was filtered free of solids under a N_2 atmosphere, washed with THF, and the filtrate and washings combined and stripped of solvent under vacuum. The residue was distilled in a KugelRohr apparatus and the solid distillate recrystallized from EtOAc/hexane to give 0.24 g (52%) 3-[2-(diethylamino)ethyl]-4-

indolol (4-HO-DET) as white crystals with a mp of 103-104 °C. The product discolored quickly in the presence of air, and was best stored under an inert atmosphere at -30 °C. Conversion to the phosphate ester was achieved by reaction of the sodium salt of 3-[2-(diethylamino)ethyl]-4-indolol with dibenzyl-chlorophosphonate, followed by the reductive removal of the benzyl groups with catalytic hydrogenation, as described for psilocybin.

DOSAGE: 10 - 25 mg, orally (as the indolol, the acetate or the phosphate)

DURATION: 4 - 6 h

COMMENTS: (with 15 mg indolol, orally) "This was in a gelatin capsule and it came on from a half hour to the three-quarter hour point like gang-busters. Time really slowed down, with sparkly-ness, interesting, and yet there was a touch of sadness. The intense visuals held the scene, and there was the compulsion to talk and to interact and to share stuff, but the erotic was not to be found. I slept OK but there was something uncomfortable at a deep level. Am OK."

(with 15 mg phosphate ester, orally) "It is meaningful to say that I ceased to exist, becoming immersed in the ground of Being, in Brahman, in God, in 'nothingness,' in Ultimate Reality, or in some similar religious symbol for oneness. The feelings I experienced could best be described as cosmic tenderness, infinite love, penetrating peace, eternal blessing and unconditional acceptance on one hand and, on the other, as unspeakable awe, overflowing joy, primeval humility, inexpressible gratitude and boundless devotion. Yet, all of these words are hopelessly inadequate and can do little more than meekly point toward the genuine, inexpressible feelings actually experienced. It is misleading even to use the words, 'I experienced,' as during the peak of the experience (which must have lasted at least an hour) there was no duality between myself and what I experienced. Rather, I was these feelings, or ceased to be in them and felt no loss at the cessation. Four days after the experience itself, I continue to feel a deep sense of awe and reverence, and am simultaneously intoxicated with an ecstatic joy. This euphoric feeling is in no sense analogous to hebephrenic giddiness; it includes elements of profound peace and steadfastness, surging like a spring from a depth of my being which has rarely, if ever, been tapped prior to the drug experience."

(with 20 mg indolol, orally) "I felt this faster than psilocin, but being twenty mg this is probably less potent."

(with 20 mg acetate ester, orally) "A mild stomach discomfort for twenty minutes, followed by intoxication to the 40 minute point. A strange mixture of things at one hour, sedation, jaw-tightening, and a generalized body tremor. The light from the fireplace gave me bursts of color. Music let me drift with my thoughts. Anorexia was intense, in fact there was some gut disturbance throughout the day, plus a lot of diuretic effect. Four hours into it I was fine on the telephone to a friend who knew nothing about the day."

(with 25 mg acetate ester, orally) "There was nausea and motor incoordination going into this. And my blood pressure went up a bit. The mental part of it all peaked at 90 minutes and all closed-eye effects had stopped after three hours. Another couple of hours and the body seemed to be OK again. Sleep OK, too. I am not impressed with this stuff."

EXTENSIONS AND COMMENTARY: On the topic of psilocybin and psilocin, one of the most frequent questions I am asked is, "Isn't it true that psilocybin is immediately converted to psilocin in the blood stream, and so the two chemicals are in essence identical, molecule for molecule?" At this moment I always suppress a brief sense of mental fragmentation, with the automatic reply, "Where is the evidence that psilocybin is converted to psilocin in man?" If it exists, I certainly do not know of it. This clears my conscience. I really do not know the answer. But I have a tremendously strong suspicion that it really does. Any such ester, be it the phosphate, the sulfate, or the acetate, would all be easily split to the archetypal indolol by the ubiquitous esterases in the body. I do indeed believe, in my inner heart, that they all act upon the brain as the same end product, psilocin. And here, with the N,N-diethyl homologue, the same arguments probably hold as well.

The ratios of molecular weights for these ethyl homologues, 314 for the phosphate (CEY-19), the same for the sulfate (by the way, it's not yet explored in man, to my knowledge), 276 for the acetate and 234 for the free phenol (CZ-74), all fall into a pretty narrow range, from about 4 to 3. So, the weight of the ester component in the actual molecule being considered is a relatively minor factor in the dose calculation. I am at peace with the hypothesis that all four compounds are interchangeable in potency.

Some fascinating studies have been done in Germany where the metabolically active mycelium of some Psilocybe species have been administered diethyltryptamine as a potential diet component. Normally, this mushroom species dutifully converts N,N-dimethyltryptamine (DMT) to psilocin, by introducing a 4-hydroxyl group into the molecule by something that is probably called an indole 4-hydroxylase by the biochemists. You put DMT in, you get 4-hydroxy-DMT out, and this is psilocin. Maybe if you put Mickey Mouse in, you would get 4-hydroxy-Mickey Mouse out. It is as if the mushroom psyche didn't really care what it was working with, it was simply compelled to do its sacred duty to 4-hydroxylate any tryptamine it came across. It was observed that if you put N,N-diethyltryptamine (DET, which has not yet been found in nature) into the growing process, the dutiful and ignorant enzymes would hydroxylate it to 4-hydroxy-N,N-diethyltryptamine (4-HO-DET) a potent drug also not known in nature. This is the title drug of this commentary. Yet another beautiful burr to thrust into the natural versus synthetic controversy. If a plant (a mushroom mycelium in this case) is given a man-made chemical, and this plant converts it, using its natural capabilities, into a product that had never before been known in nature, is that product natural? What is natural? This is the stuff of many long and pointless essays.

A valuable concept was championed by one of the most respected psychotherapists and academicians in recent years, Hanscarl Leuner, the Chairman of the Psychotherapeutic Department of the University of Göttingen, Germany. Leuner was convinced that the value of the psychedelic drug was in the opening of the psyche with repeated modest exposures, with therapy carried forth over a period of time. This is the "psycholytic" approach to therapy. An opposite approach is called "psychedelic." Here there is what might well be a one-time interaction, in which the patient is blasted into orbit with the hopes of his confronting his problem and also finding its solution. When LSD is used in the former approach, in psycholytic dosages, one would expect levels of between 50 and 150 micrograms to be used; in the latter (psychedelic) approach, the dosage would be in the 500 to 1500 microgram range. The first calls upon the activation and development of a process of understanding; the second can be seen as a religious crisis, or a conversion event. In Europe, the first was favored, but there were strong advocates (Unger, Pahnke, Grof) in the United States favoring the latter process. Here, CZ-74 was thought to be suitable only in the psycholytic role, in that it was too short lived and, at high doses, there was a restlessness and body disturbance that was not usually seen with LSD.

There is a second instructive point to be learned from Leuner. It was he who had made early observations of the psychological effects of CZ-74 in man (within two years of the reported synthesis in about 1959) and had carried out the most extensive clinical studies ever conducted, involving at least 160 trials in human volunteers. He presented two separate reports in 1965, to two very different audiences. To the psychotherapeutic audience there was a strong emphasis made of the psycholytic virtues to be found in CZ-74, including its very short duration and the positive nature of the experience. The sessions were called "overwhelming and ecstatic" with the "elimination of the hangover of LSD — or any pathological after-effects — even with dosages of up to 40 milligrams." The plaudits continued: "Thus, this drug must be considered to be particularly safe and suited for ambulant psycholytic treatment and use by psychiatrists in their practices." Almost everything was positive.

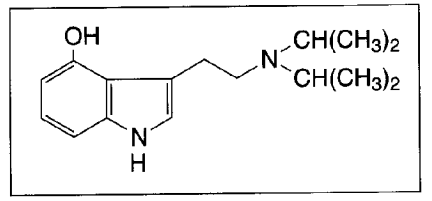
However, in addressing a neurosciences conference, also in 1965, and referring to the same studies and the same experimental population, he reported some pretty heavy-duty neuropharmacological negatives. "In all sessions there were disturbances of body image, illusions, pseudo-hallucinations and hallucinations. In 50% of [the] cases, motor restlessness, aphasia, loss of concentration and temporal and spatial disorientation could be clearly observed. In 25% of the cases there was loss of impetus, derealization and acoustic hallucinations. More rarely and only with the highest doses did extreme psychotic symptoms occur, with increased volubility, depersonalization, cosmic-mystic experiences, delirium, schizophrenic behavior with catatonic fits and temporary paranoia." Almost everything was negative.

At a banquet associated with an international conference on the study of consciousness, held in Göttingen a few years ago, Alice and I had the pleasure of sitting at the table with Hanscarl Leuner and his wife. He thanked me for inventing 2C-D, which he and his students had been exploring as an adjunct to psychotherapy. They had renamed it, initially DMM-PEA and then LE-25, and had apparently explored it at dosages that reached into the hundreds of milligrams. In *PIHKAL*, I had offered an effective range for this drug of from 20 to 60 milligrams. It would seem that in his later years, Dr. Leuner chose to move from the psycholytic camp over to the psychedelic camp.

One final comment. When you read a paper or listen to a lecture offered by a researcher of impeccable qualifications, take a moment to look about you to see who is alongside you in the audience that is being addressed. Who else is reading his paper? Who else is hearing his lecture? How might the presentation be tailored to fit the interests of the recipients? The identification and recognition of your neighbors should play a role in your evaluation and acceptance of the presentation.

#17. 4-HO-DIPT: TRYPTAMINE, N,N-DIISOPROPYL-4-HYDROXY; 4-INDOLOL, 3-[2-(DIISOPROPYLAMINO)ETHYL]; N,N-DIISOPROPYL-4-HYDROXYTRYPTAMINE; 3-[2-(DIISOPROPYLAMINO)ETHYL]-4-INDOLOL

SYNTHESIS: A solution of 0.50 g 4-acetoxyindole (see under 4-HO-DET for its preparation) in 5 mL Et_2O was stirred and cooled to 0 °C with protection from atmospheric moisture. There was then added 0.5 mL oxalyl chloride. The reaction mixture was stirred for an additional 30 min, and the intermediate indoleglyoxyl chloride separated as a yellow crystalline solid but not isolated. This was treated with a 40% solution of diisopropyl amine in anhydrous Et_2O, dropwise, until the pH was 8-9. The reaction was diluted with 100 mL $CHCl_3$ and shaken with 30 mL of a 5% aqueous $NaHSO_4$ followed by 30 mL of a saturated aqueous $NaHCO_3$ solution. After drying over anhydrous $MgSO_4$, the organic solvents were removed under vacuum. The residue was recrystallized from EtOAc/hexane to give 0.33 g (35%) of 4-acetoxyindol-3-yl-N,N-diisopropylglyoxylamide, mp 204-206 °C. Anal: C,H,N.



To a stirred suspension of 0.25 g LAH in 10 mL anhydrous THF, stirred, under nitrogen and at room temperature, there was added a solution of 0.30 g 4-acetoxyindol-3-yl-N,N-diisopropylglyoxylamide in 10 mL anhydrous THF. This was added, dropwise, at a rate that maintained the reaction at reflux. When the

addition was complete, the reflux was maintained for an additional 15 min and then the reaction was cooled to 40 °C. The excess hydride and the product complex were destroyed by the addition of 0.5 mL EtOAc followed by 1.5 mL H_2O. The solids were removed by filtration, the filter cake washed with THF, the filtrate and washings pooled, and the solvents removed under vacuum. The residue was distilled at the KugelRohr and the distillate dissolved in 1 mL MeOH. One equivalent of dilute HCl was added, and the volatiles were removed under vacuum. The solid residue was recrystallized from MeOH/Et_2O to give 0.12 g (44%) of 4-hydroxy-N,N-diisopropyltryptamine hydrochloride (4-HO-DIPT), mp 263 °C with decomposition. Anal: C,H,N.

DOSAGE: 15 - 20 mg, orally

DURATION: 2 - 3 h

QUALITATIVE COMMENTS: (with 10 mg, orally) "I feel it in my legs! Within the hour I have leg tremors, a mild physical awareness for another hour. Mentally, probably nothing."

(with 15 mg, orally) "There was an alerting, noisy and nice, in 30 minutes. I swear I am already there. Nice friendly place. Perhaps some light tension, like a chill, maybe my body temperature response is confused. At the two hour point I am substantially out of the experience. Short, intense experience, basically enjoyable. Another hour and I am back to where I started in every way."

(with 20 mg, orally) "It has a bitter taste. Early signs noted at 15-20 minutes which include mild sensation of central stimulation, 'loosening' of muscles in arms, legs, and neck. Mild distortion of objects and slight color effects, typically 'rainbow halos' around objects. Plateau reached in 20 minutes. Mild elation with relatively simple intellectual musings about the nature of the compound and how one could describe the nature of the state of mind and body caused by this material. 2.0 hours, mild effects. 2.5 hours, nearly normal. Mild but entirely pleasant experience with rather abrupt termination of effects. Could be a good candidate for psychotherapy sessions, certainly good for 'novice' introduction to hallucinogens."

(with 20 mg, orally) "Fifteen minutes, it starts and develops fast — very nice — some leg tremor. Thirty minutes, I am already well over a plus 2. Speed of onset is incredible — I could not drive — I feel robbed of voluntary action. Forty minutes, this could not get any deeper. Fifty minutes, incredible orgasm. Fifty five minutes, I struggle to put a name to it, just +++ smashed — with eyes closed very little — I am somewhat chilled — no visual, no sensory, this seems like an extreme Aleph-7 Beth state (see Places in the Mind, chapter 10). One hour ten minutes, Rubenesque fancy — no sex but back-to-mother cuddly imagery — removed from physical angles. One hour thirty minutes, go for two very significant pieces of wood for the fireplace — if all my actions are preprogrammed and I am following commands, then I have no free will — if the command is 'to have free will', then I obey. Whom? Who? Why obey an undefined, unheard commander? Still +++. Nothing is inventive, all is preprogrammed. One hour forty minutes, back to ++, still very much in the grips of 'lack of self determination.' I could function rationally in the lab, but following 'whose' directions? Is this finally God? Is this a religious experience? One hour fifty minutes, down to +. This has to have been a religious awakening. Two hours, still a little zombie-like, but largely down. Two hours twenty minutes, I am still shaken to my roots by these realizations. Three hours, completely together."

EXTENSIONS AND COMMENTARY: I truly doubt that there is another psychedelic drug, anywhere, that can match this one for speed, for intensity, for brevity, and sensitivity to dose, at least one that is active orally. These reports have been taken from different experimenters, but they share some rather consistent features:

Speed: The effects are noted within a quarter hour following ingestion. LSD is one of the few psychedelic drugs that can show its early effects in the first few minutes. This suggests fundal absorption.

Intensity: The second 20 milligram report sounds as if there was some flirting with the magical plus-four transcendental peak experience. I happened to be the subject, and I was impressed.

Brevity: To be on a trip and then to be back pretty much in two hours and really baseline in another hour? Most unusual. If there will ever be an acceptance of drugs such as these, in a psychotherapeutic context, a short duration is of extreme value to both the patient and the therapist.

Sensitivity to dose: There have been a number of trials at and below the 10 milligram bottom, and most have been substantially without activity. And yet, there have been no trials at higher than 20 milligrams, as far as I know. That is a lot of steepness in the dose-response curve.

And similar comments can be made regarding the consistency of physical side-effects. There seemed to be a muscular tremor, and a vague body malaise, that is part of the trip. At least when the psyche got going, the body was less noticeable.

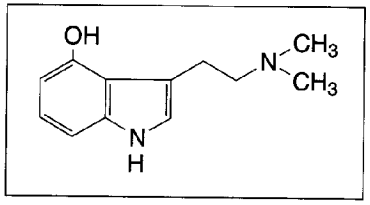
An interesting sideline. This is the same nitrogen substitution pattern, N,N-diisopropyl, that is present in the rather dramatic sex-enhancer 5-MeO-DIPT. I wonder what might come out of an exploration of this substitution pattern in the world of the phenethylamines? As a rule, most phenethylamines lose their appeal with substitution on the nitrogen atom. But has anyone tried to make an N,N-diisopropyl homologue of MDMA, for example? Or of mescaline? Or of DOM? It would be interesting to explore these areas.

#18. 4-HO-DMT; TRYPTAMINE, 4-HYDROXY-N,N-DIMETHYL; 4-INDOLOL, 3-[2-(DIMETHYLAMINO)ETHYL]; N,N-DIMETHYL-4-HYDROXYTRYPTAMINE; 3-[2-(DIMETHYLAMINO)ETHYL]-4-INDOLOL; CX-59; PSOH; PSILOCIN

4-HO-DMT PHOSPHATE ESTER; TRYPTAMINE, N,N-DIMETHYL-4-PHOSPHORYLOXY; 4-INDOLOL, 3-[2-(DIMETHYLAMINO)ETHYL], PHOSPHATE ESTER; N,N-DIMETHYL-4-PHOSPHORYLOXYTRYPTAMINE; 3-[2-(DIMETHYLAMINO)ETHYL]-4-INDOLOL, PHOSPHATE ESTER; CY-39; PSOP; PSILOCIN, PHOSPHATE ESTER; PSILOCYBIN

SYNTHESIS: To a solution of 0.50 g 4-acetoxyindole (see preparation in the recipe for 4-HO-DET) in 4 mL Et_2O that was stirred and cooled with an external ice bath there was added, dropwise, a solution of 0.5 mL oxalyl chloride in 3 mL anhydrous Et_2O. Stirring was continued for 0.5 h and the intermediate indoleglyoxyl chloride separated as a yellow, crystalline solid but it was not isolated. There was then added, dropwise, a 40% solution of dimethylamine in Et_2O until the pH came to 8-9. The reaction was then quenched by the addition of 100 mL $CHCl_3$, and the organic phase was washed with 30 mL of 5% $NaHSO_4$ solution, with 30 mL of saturated $NaHCO_3$, and finally with 30 mL of saturated brine. After drying with anhydrous $MgSO_4$, the solvent was removed under vacuum. The residue set up as crystals and, after recrystallization from THF, provided 0.61 g (80%) 4-acetoxyindol-3-yl-N,N-dimethylglyoxylamide with a mp of 204-205 °C. Anal: C,H,N.

A suspension of 0.38 g LAH in 10 mL anhydrous THF was held in an inert atmosphere and vigorously stirred. To this there was added, dropwise, a solution



of 0.55 g of 4-acetoxyindol-3-yl-N,N-dimethylglyoxylamide in 10 mL anhydrous THF at a rate that maintained a gentle reflux. After the addition was complete, the refluxing was maintained for an additional 15 min, the reaction mixture cooled to 40 °C, and the excess hydride destroyed by the addition of water diluted with a little THF. The reaction mixture was filtered free of insoluble material under a N_2 atmosphere and the resulting solids washed with THF. The filtrate and washings were combined and stripped of solvent under vacuum. The residue was distilled in a KugelRohr apparatus and the solid distillate recrystallized from EtOAc/hexane to give 3-[2-(dimethylamino)ethyl]-4-indolol (4-HO-DMT, psilocin) as a white oil which solidified. Recrystallization from EtOAc/hexane gave white crystals which had a mp of 103-104 °C. The final weight was 0.23 g (yield 56%). IR (in cm^{-1}): 686, 725, 832, 991, 1040 and 1055; the OH stretch is at 3240. MS (in m/z): $C_3H_8N^+$ 58 (100%); parent ion 204 (15%); indolemethylene+ 146 (3%); 159 (2%).

Most of the early syntheses of psilocin and psilocybin use the O-benzyl ether as a protecting group. This provides more stability to the chemical intermediates, but also requires the additional step of reductive debenzylation. The flow chart of this process is: conversion of 4-hydroxyindole to 4-benzyloxyindole via the sodium salt, with benzyl chloride; the conversion of this with oxalyl chloride to 4-benzyloxyindole-3-glyoxylchloride; the conversion of this to 4-benzyloxyindole-3-(N,N-dimethyl)glyoxamide with anhydrous dimethylamine; the conversion of this to 4-benzyloxy-N,N-dimethyltryptamine with LAH in dioxane; and finally the conversion of this to 4-HO-DMT (psilocin) with hydrogen with a Pd catalyst on Al_2O_3. The phosphate ester, psilocybin, requires two additional steps: the conversion of 4-HO-DMT (as the sodium salt) to 4-(O,O-dibenzylphosphoryloxy)-N,N-dimethyltryptamine, with dibenzyl chloro-phosphonate, followed by the catalytic removal of the benzyl groups with hydrogen and Pd on Al_2O_3 to give the phosphate ester of 4-HO-DMT (psilocybin). This product is much more stable in air than psilocin, and is water soluble. The yields of this conversion are, however, very bad, often less than 10%, and the two products appear to be pharmacologically equivalent. Further, I have heard that the phosphorylating agent dibenzyl chlorophosphonate must always be used in solution as it is quite unstable as a pure reagent. The fingerprint infra-red spectrum for psilocybin shows (in cm^{-1}): 752, 789, 806, 858, 925 and the P=O stretch at 1110; the acidic OH stretches are broad peaks at 2400, 2700 and 3200. The mass spectrum is identical to that of psilocin.

DOSAGE: 10 - 20 mg, orally (as the indolol, the acetate or the phosphate)

DURATION: 3 - 6 h

QUALITATIVE COMMENTS: (with 6.6 mg phosphate ester, orally) "Something has started but I decide to join in a full dinner anyway. The effects develop right through the meal, with some hints of animal faces in the pork-chop bones. No movement, nothing flows, but it probably wouldn't take much effort. Another hour and I am dropping off already. The food? Somehow I doubt it. I would be completely unable to tell this from, say, 80 milligrams of MDMA except that I had a good appetite."

(with 7 mg, orally) "Basically I am not in a pleasant place — quite neurotic — inwardly turned — a touch of despair — considerable visual activity and if I were with someone I might find some sort of reinforcement. The apathy and unpleasantness is ebbing now. My mood might have been negative, and the psilocybin simply amplified everything. There was some intensification of the lights and darks around me."

(with 10 mg, orally) "Approximately forty minutes after the start, there was a flutter and a very high, stimulated feeling, and gradually things began to move very rapidly. It was astounding. When I closed my eyes I saw so many fantastically

beautiful patterns, textures, colors. Everywhere I looked, eyes open, colors were brilliant. The house looked absolutely gorgeous, nature was simply spectacular. It was a little frightening, almost too exciting, after the gentleness of other substances. I could not believe that I was doing it, and that I had the power within myself to see such beauty. I don't know how long this went on but the motion was so rapid that I felt a sort of motion sickness. Then I became quite nauseated and remained nauseated the rest of the day, until things quieted down in the evening, and then I felt absolutely wonderful."

(with 15 mg, orally) "My 'early warning system' alerted me at fifteen minutes, then all was quiet for a while. I start building up again, and I am awfully glad that I am familiar with this transition. Visual distortions. Things distract me. I can't find the cap to my pen — must I keep writing forever? At this point I couldn't drive, let alone write, and it is just a bit more than a half hour since I took it. The furniture in my office is moving up and down. I lie down, and close my eyes. THIS is where it is at. Visuals are wild. Even with eyes open, with no visual target, there are imaginative visual effects. I imagine a dark room with a fire place going in the middle of the night, with no other inputs, and with my eyes closed I have the body image of being seated in front of that fire and I am amazed by the hallucinations and distortions I am seeing there only there is no fireplace as I am still lying in my darkened bedroom. Sort of a 2x removed hallucination. This is a night-time drug — the day-light washes everything out. I tried but could not repeat the fireplace thing, and must be dropping rapidly. At three hours I ask if I would try some other experiment. OK, but there are some reservations. At four hours, no reservations."

(with 15 mg, orally) "As soon as I felt the chill and the alert, I lay down and closed my eyes. Indian motif. Abundant fruits, vegetables, leaves, straw, wood, vines. Very responsive sexually. Beautiful, stern, rich encounter with livingness and Indian Gods and serenity. Color and peacefulness. A couple of hours, then elaborateness dropped slightly. At this point top of temple easy, but it was a South American temple, with earth floor, straw, vines full of fruit. Familiar feeling. We are naked and we are children-adults, daring to be there, regarded benignly (stern, amused) (rising through the floor). This is one of the true ones, this plant experience.

(with 12 mg phosphate ester, intramuscularly) "This is strong. There were a lot of wild images in about two hours, and I thought that the day would never end. At about six hours I knew it would, but in fact in the evening I took 100 milligrams of Seconal which allowed me to drift into a fine sleep. The next day I was fine."

(with 3 mg phosphate ester, intravenously) "The effects are immediate (in 30 seconds) and I did not have the time to build up any worry — it was simply too fast. In about an hour I was back where I started from."

(with 12 mg phosphate ester, intravenously) "I had had eight milligrams earlier, with a very good reaction. Here, today, I feel that everything has disintegrated, and I am extremely anxious. I am very confused."

Psilocybe cubensis: (with 1.5 g, orally) "At best, some speckled patterning with my

eyes closed, and in general a light intoxication. Certainly not the sparkle of LSD. Dropped quickly and felt heavy and tired, good sleep."

(with 3.5 g, orally) "Took a gram to start with, and it started in ten minutes, but not strong enough, so did the other 2.5 grams. Everything was coming at me in waves, boxing me in, the visuals were in waves and in dark earth colors, orange and brown, not the wide spectrum of acid. I was sea-sick, and vomiting helps some, and a little dope quieted the tummy. Started dropping, and everything became very good, and by midnight I was out. No hangover at all."

EXTENSIONS AND COMMENTARY: There are two generalizations implicit here, one of which I am quite at peace with, but the other is both complex and disturbing. The OK item is the casual equation between the hydroxy compound psilocin, the acetate ester, and the phosphate ester, psilocybin. As I had discussed in the CZ-74 to CEY-19 entries in 4-HO-DET, there is no proof that the ester goes to the indolol metabolically, but it is a good guess, and there have been no demonstrated differences in their pharmacology. Ditto here, with psilocin and psilocybin. I have explored both of them as pure chemicals, and I find them completely interchangeable as to their pharmacological properties.

The second generalization is more difficult and leads into some uncomfortable areas. This is the effort to equate the chemicals, psilocin and psilocybin, with their natural sources, the mushrooms. Part of the uncertainties I feel are related to the unknowns that are intrinsic to the plant sources. There are many species that have been offered and accepted as magic mushrooms. Identification in the field is one thing, but what can be said of dried, ground up plant material of unknown sources? What are they? How have they been preserved? What is their composition? The older samples may be reasonably free of the rather unstable psilocin, but psilocybin is much more stable and may persist. But so might its congeners such as baeocystin and norbaeocystin which are scattered in widely different proportions in many species, and which are quite unexplored pharmacologically. The same instability certainly applies to the dephosphoralated psilocin analogues 4-HO-NMT and 4-HO-T. These both could well be metabolites of psilocin in man. There are so many uncontrollable variables in the mushroom area that here I cast my vote for exploration with the chemicals themselves. They can, at least in principle, be analyzed, and weighed. But this is a luxury not available to many, as the synthesis of these alkaloids is difficult, and woefully illegal.

Which brings us back to the mushrooms, and the topic of the law. In the original writing of the Controlled Substances Act of 1970, our Federal drug law, there are only four plants listed as being "Scheduled Drugs." In Schedule I there was Marijuana (later defined as the plant *Cannabis* spp.) and Peyote (later defined as the botanical *Lophophora williamsii*); in Schedule II there was Opium poppy and poppy straw, and Coca leaves. It is generally known that commercial opium comes from the plant *Papaver somniferum* and that commercial coca comes from the plant *Erythroxylum coca*, but I am not aware of either of these botanical binomials having

been explicitly named in the statutes. A couple of quickies were slipped in, not completely properly, in the giving of the binomial of *Tabernanthe iboga* as a synonym for ibogaine, and the giving of the binomial of *Catha edulis* as a synonym for cathinone, both Schedule I drugs. So there are definitely four, and maybe six, plants that can be considered scheduled drugs.

But nowhere in the legal archives of current drug statutes can you find mention of Genera such as *Psilocybe*, *Stropharia*, *Paneolus* or *Inocybe*. Nor of the dozens and dozens of species that stem from them. So, you would logically conclude that these magic mushrooms are not illegal? Well, yes and no.

No, in the letter-of-the-law sense that they are not explicitly named as illegal entities. But yes, in the *de facto* exercise of the law. With the inescapable fact that both psilocin and psilocybin are named as Schedule I drugs, and the acknowledgment that there are some mushrooms that might contain these drugs, then these botanical entities become legal complications. Might the dried fruiting bodies be seen as packaging strategy for the sale and delivery of a Schedule I drug? Might the growing of them be seen as a production strategy for the manufacture of a Schedule I drug? Of course it might be, as the law has stated that the manufacture and sale of Schedule I drugs is a Federal felony. "Your Honor. I gathered these things out there in the field for my dinner salad. I had no idea that they contained something illegal." A reasonable defense, and it may well work today, along with the argument that opium poppy pods are buyable at the Farmer's Market as floral decorations, and morning glory seeds can be bought at the local nursery for next Spring's garden. Innocence may be a virtue for a while, as it is not widely recognized that these decorative poppies are in fact Schedule II opium capsules and those *Ipomoea* seeds in fact contain ergine, a Schedule III depressant. But that is today. What happens tomorrow?

Today, to a large measure, the burden of proof still falls upon the accuser, and that ephemeral and undocumented "presumption of innocence" concept provides some measure of protection. They, the accusors, must prove you are guilty. But, as the legal structure drifts from the criminal statutes to the regulatory statutes, this protection is lost. You must prove that you are innocent. The perfect example is the random urine test, which demands, without any probable cause, that you prove that you do not have drugs in you. There is no presumption of innocence. This has been the sad state of our income tax laws for years, and now it is becoming a reality in our drug laws. Prove to the court that you didn't know that these mushrooms were psychoactive! Shades of the Inquisitions of a few hundred years ago. Or the Salem travesties of more recent times. Prove to us you are not a witch.

There is quite a body of scientific literature that discusses the changes (increases and well as decreases) of psilocybin and psilocin content in mushrooms as a function of their nutrient diet. And, under the 4-HO-DET entry, I mentioned that the inclusion of an unnatural component into the diet just might produce an unnatural alkaloidal product, with an exploitation of the natural and available

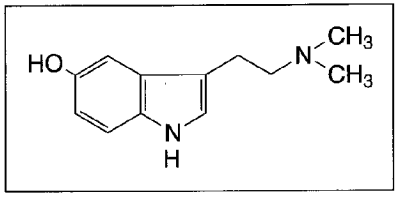
enzyme systems that are part of the mycelial structure.

Another aside. There is a trivial, and fun, bit of nomenclature which I have used for years. I have, in my notes, referred to psilocybin as PSOP (because of the phosphate thing) and psilocin as PSOH (because of the exposed OH group). I have gotten into the habit of referring to the acetate as PSOA, the O-methyl ether as PSOM and the chemical intermediate O-benzyl ether as PSOB. I know that this will never catch on, but I still do it because it is convenient and a bit campy. One code that is not mine, but Sandoz's, is CMY for 1-methyl-psilocin. I know it has been looked at in a clinical environment, but I have no idea as to its activity. It is a straightforward thing to make. I would love to know what it does.

#19. 5-HO-DMT; TRYPTAMINE, N,N-DIMETHYL-5-HYDROXY; INDOL-5-OL, 3-[2-(DIMETHYLAMINO)ETHYL]; N,N-DIMETHYL-5-HYDROXYTRYPTAMINE; 3-(2-DIMETHYLAMINOETHYL)INDOL-5-OL; N,N-DIMETHYLSEROTONIN; BUFOTENINE; MAPPINE

SYNTHESIS: A solution of 0.67 g 5-hydroxyindole (indol-5-ol) in 10 mL dry MeOH was treated with a solution of 0.30 g NaOMe in MeOH, followed by 0.70 g benzyl chloride. The mixture was heated on the steam bath for 0.5 h, and the solvent removed under vacuum. The residue was suspended between H_2O and CH_2Cl_2, the organic phase separated and the aqueous phase extracted once with CH_2Cl_2. The combined organics were stripped of solvent under vacuum, and the residue distilled. A colorless fraction came over at 170-190 °C and spontaneously crystallized in the receiver. There was obtained 0.90 g (80%) 5-benzyloxyindole with a mp 81-86 °C which increased, on recrystallization from toluene/hexane, to 94-96 °C. A sample prepared from the decarboxylation of 5-benzyloxyindole-2-carboxylic acid has been reported to have a mp of 102 °C from benzene.

A solution of 1.0 g 5-benzyloxyindole in 20 mL Et_2O was cooled to 0 °C, vigorously stirred, and treated with 0.6 g oxalyl chloride in 10 mL Et_2O, added dropwise, over the course of 0.5 h. About half way into the addition a pale red solid appeared. The stirring was continued for an additional 0.5 h and the solids were removed by filtration and washed with a small amount of Et_2O. This acid chloride had a mp of 149-151 °C and was used without further purification or characterization in the following reaction. It was added in small increments to 1.2 mL of a 33% aqueous solution of dimethylamine, diluted with acidified H_2O, and the resulting solids removed by filtration. These were washed with H_2O, and then Et_2O and air dried. The product,



5-benzyloxy-N,N-dimethyl-3-indoleglyoxylamide weighed 1.18 g (82%) when dry and had a mp of 185-187 °C.

To a well-stirred suspension of 1.0 g LAH in 40 mL Et_2O there was added a solution of 1.0 g 5-benzyloxy-N,N-dimethyl-3-indoleglyoxylamide in 15 mL THF. When the addition was complete, the mixture was held at reflux temperature for 6 h, cooled, the excess hydride and reaction complex cautiously decomposed by the addition of H_2O, and when the hydrogen evolution ceased the mixture was made basic with concentrated NH_4OH. The solids were removed by filtration and the filter cake washed with THF. The filtrate and washings were combined, and the solvents removed under vacuum to give a clear residue that was dissolved in Et_2O and acidified with a solution of oxalic acid in Et_2O. The formed crystals were removed by filtration, washed with Et_2O and air dried to yield 1.0 g (84%) of 5-benzyloxy-N,N-dimethyltryptamine oxalate with a mp of 178-180 °C after recrystallization from MeOH. The hydrochloride salt has a reported mp of 154-155 °C, and of 162-163 °C.

The benzyl group was removed by hydrogenation of a solution of 0.8 g 5-benzyloxy-N,N-dimethyltryptamine oxalate in 5 mL MeOH containing 0.1 g 10% Pd/C catalyst. The mixture was shaken under three atm hydrogen for 6 h, and the solids removed by filtration. Evaporation of the solvent under vacuum gave a residue that was dissolved in anhydrous Et_2O and acidified with a solution of oxalic acid in Et_2O. There was thus obtained, after filtration, Et_2O washing, and air drying, 0.53 g (87%) bufotenine mono-oxalate as pink needles, with a mp 93-94 °C. A mp of 178 °C in the literature may be of the bioxalate. The free base has been reported to have a mp of 125-126 °C or 146-147 °C.

DOSAGE: 8 - 16 mg, intravenously

DURATION: 1 - 2 h

QUALITATIVE COMMENTS: (with 1 mg, intravenously, over a three minute period) "Within a minute (from the start of the injection) I had a tight feeling in my chest and my face felt as if it had been jabbed by nettles and this lasted for about 6 minutes. I had fleeting nausea."

(with 2 mg, intravenously, over a 3 minute period) "I felt a tightness in my throat and stomach and it seemed that my pulse was racing, although apparently there was no change in either my pulse or blood pressure."

(with 4 mg, intravenously, over a 3 minute period) "During the injection, I first felt a burning sensation in my face, then a load pressing down from above, and then a numbness of the entire body. I saw red and black spots — a vivid orange-red — moving around. Apparently my purplish face color lasted some 15 minutes, well after my visual things had disappeared."

(with 8 mg, intravenously, over a 3 minute period) "I became lightheaded

as soon as the injection started, and then my face turned purple and I became nauseated and I felt I couldn't breathe. I see white, straight lines with a black background. I can't trace a pattern. Now there are red, green and yellow dots, very bright like they were made out of fluorescent cloth, moving like blood cells through capillaries, weaving in and out of the white lines. In another two minutes, everything was pretty much gone."

(with 10 mg, intravenously, over a 50 second period) "My face was suddenly very hot. I could not breathe fast enough."

(with 10 mg, intravenously, over a 77 second period) "There were no psychological changes."

(with 16 mg, intravenously, over a 3 minute period) "Almost immediately I felt a burning sensation in the roof of my mouth and I felt a tingling all over my body. My face turned purple, and my chest feels crushed. Everything has a yellow haze, and I was sweating heavily and I vomited. Words can't come. My mind feels crowded. When I start on a thought, another one comes along and clashes with it. I can't express myself clearly. I am here and not here. It has now been forty minutes and I feel better, but I still feel like I would like to walk it off, like a hang-over."

EXTENSIONS AND COMMENTARY: This is a presentation of the very earliest studies done with bufotenine with human subjects, studies with 14 schizophrenic patients at a state mental hospital and with two convicts in a state prison. The two convicts were injected over the course of three minutes, with a solution of bufotenine as the salt. This single observation, a description of hyperserotoninemia (a release of serotonin in the blood, called a carcinoid flush) was all it took, at the right time and the right place, to put bufotenine on the books as a "dangerous drug" by FDA classification. And with the passage of the Controlled Substance Act of 1970, it was placed in Schedule I as a hallucinogen, with a high abuse potential and no accepted medical utility. Whatever the actual activity of bufotenine might be, and what role it could play in explaining the complex role of serotonin in the human animal, today it would be extremely difficult to study, because of the flushing of the face of an experimental subject in a prison in Maryland in a study that occurred at just the wrong time.

But that is the politics of the drug. I cannot help but comment on some aspects of the medical ethics that accompanied these studies. Here were a collection of 14 schizophrenic patients—experimental cattle is the analogy that comes to mind — into which the researching physicians injected their drug. Listen to the account of one lady, following a rapid intravenous injection of bufotenine. "There was intense salivation. She could easily have drowned in her own saliva, and she had to be turned on her side. The pulse rate rose slightly during the period extending from the end of the injection until some 10 minutes later, but without much change in blood pressure. Responsiveness returned in about 23 minutes, at which time the patient was entirely lucid and, in response to a query related to a preinjection

suggestion, spoke of a long-repressed memory from the age of three years, when she came into the bathroom and saw her mother dying of a uterine hemorrhage. This was told without affect and had no therapeutic consequences." HOLY COW! A schizophrenic victim volunteers a long-repressed memory of her mother's traumatic death. And with the state of the healing art in the mental hospitals of that time, two physicians effectively ignored what today would be considered a dramatic breakthrough in therapy. Another of their trials was acknowledged as being nearly fatal, requiring artificial respiration as intervention. This is research in the healing art of medicine?

So much for the politics, and for the medical ethics lecture. What can one say about the drug itself? This is an example of a very rare breed of active compounds, one that can be found in both the animal and the vegetable kingdoms. From toads to toadstools. There are a number of extremely close structural relatives out there in the wild world. Bufotenine must first and foremost be seen as an extremely close relative to serotonin (one of our principal neurotransmitters) of which it is the N,N-dimethyl homologue. There are many modifications of it in nature (found most frequently in the skins of frogs), and these all have deceptively similar names. It is helpful to me to tally them.

Bufoviridine: This is the 1:1 ester of bufotenine with sulfuric acid. It is yet more polar than bufotenine, and correspondingly less likely to get into the brain. If the bisulfate acid position were itself esterified in some biologically stable manner, then this compound just might be centrally active, but probably only via a parenteral route as seen with 5-MeO-DMT. The exposed dimethylamino group would still make it an easy substrate for MAO's.

Bufotenidine or Cinobufagine: This is the quaternary amine internal salt, 5-hydroxy-N,N,N-trimethyltryptammonium salt. It also is frequently found as a hydrogen sulfate ester, but this latter has no trivial name. Mention has been made of bufotenidine and its sulfate ester as an occasional companion of histamine analogues found in frog skins. See the appendix on histamines.

Dehydrobufotenine: There is a covalent bond formed between the dimethylated nitrogen atom and the indolic 4-position, by the theoretical removal of a molecule of hydrogen. It is no longer a simple tryptamine but as it is a commonly found component of the chemistry of several toads, and a few giant reeds as well, it is included here. It is, by definition, a quaternary amine salt. The original structure assigned it was that of a vinylamine (with the loss of a hydrogen molecule from the alpha/beta chain positions). This was shown to be incorrect.

Bufothionine: This is the hydrogen sulfate ester of dehydrobufotenine.

O-Methylnordehydrobufotenine: This is a rearrangement product of dehydrobufotenine, which may be a natural product or it may be an artifact of analysis.

O-Methylbufotenine: This represents a true crossover alkaloid, found in many plants as well as in the toad family. It is entered as a recipe under the synonym 5-MeO-DMT.

Norbufotenine (5-hydroxy-N-methyltryptamine, N-methylserotonin, 5-OH-NMT): This base is scattered in both the animal and the plant kingdoms. It has been found in quite a few toads and in barley shoots. It has been isolated from the herb *Desmodium pulchellum*. This is an interesting twilight compound lying half way between a notorious toxin (bufotenine) and a vital neurotransmitter (serotonin). And it is unexplored, for shame. It has been detected in the urine of schizophrenic subjects, but that doesn't say anything about its potential activity. That bare hydroxyl group may make it difficult to get into the brain, probably as difficult as bufotenine itself proved to be. The removal of the second methyl group reveals serotonin.

Bufogenins or Bufagins: These are nitrogen-free steroidal lactones that are heart toxins found in toad venom. They have no chemical resemblance to bufotenine whatsoever. Examples are bufogenin B, bufotalin and bufotalinin.

Bufotoxins: These are steroidal bufagins, usually linked via an hydroxyl suberic acid which is, in turn, bound by a peptide link to arginine.

There are two structural variations of bufotenine that I feel would be interesting to explore. One deals with the ethers of the 5-hydroxyl group. The O-methyl ether is, of course, 5-MeO-DMT. It is mentioned above under the name O-methylbufotenine. What about the obvious O-ethylbufotenine, 5-EtO-DMT? It had once been synthesized from 5-ethoxytryptophol in a physostigmine study, and had been converted to bufotenine with aluminum chloride. If the analogy from the phenethylamines applies here (MEM is as potent as TMA-2) then 5-EtO-DMT should be as potent as 5-MeO-DMT. And probably would have to be smoked for the very same reasons. Another variation deals with possible esters on that 5-hydroxyl group. Finding activity in things like the bisulfate bufoviridine would be unlikely, but perhaps an acetate ester (easily made from bufotenine and acetic anhydride) would allow it to make it into the CNS, in a manner similar to the acetate of the 4-hydroxy analogue, psilocin.

There once was (and maybe still is) a group called The Institute of Current World Affairs who gave grants to people to allow them to travel and write on topics of cultural interest. I was on their mailing list, which gave me a fabulous collection of essays and vignettes written by Andy Weil, who later spun some of them together into a book called, *The Marriage of the Sun and Moon*. In trying to organize and understand the pharmacology of bufotenine I was pleasantly reminded of the essays Andy devoted to the magic of Uri Geller.

He was initially completely entranced by the way this young man from Israel could muster the psychic energy of an audience to bring about some remarkable phenomena. It was not just the bending of keys and spoons, but it was remote viewing and mind-reading as well. It was the stuff of the miraculous.

Andy was a total convert, but then there was an abrupt erosion of certainty that began with Andy's meeting with a skeptic called the Amazing Randi, who could duplicate most of the illusions with his sleight of hand mastery. Andy went from total belief to total disbelief in a very short period of time. It seemed that his earlier

conviction was wrong and that all was indeed misrepresentation. This change in position of course managed to offend both camps. Then he came finally to a middle ground. The status of Uri Geller may be essentially unanswerable. Psychic phenomena are believed by some. Are these things factual? Who is judging it all, and from what point of view?

And so it is with bufotenine. Is it an active psychedelic? Absolutely yes, absolutely no, and maybe yes and maybe no.

The early reports used the "psychotomimetic" term and pushed for a psychedelic interpretation of the observations. Observers saw colored spots, straight lines against a black background. "Words can't come. My mind feels crowded." These and similar descriptions are often encountered as components of psychedelic experiences. And yet a skeptic would point to the terms that are closely associated with toxic effects, and peripheral poisoning: my face turned purple and I became nauseated, I could not breathe fast enough. Lacrimation and tachycardia. These all are excerpts from the small selection of comments given above. In the period that has followed the earliest studies described in the "Qualitative Comments" section above, there have been about a dozen additional reports that could be offered that describe the same scatter of ups and downs, employing different modes of delivery. With insufflation, I have one that claims a feeling of fear, a flushing of the face, lacrimation and tachycardia, with ten milligrams. Another report states that after snorting forty milligrams, he observed neither objective nor subjective effects. Some clinicians declare that the compound is unquestionably a psychotomimetic and it must be catalogued right up there along with LSD and psilocybin. Others, equally sincere, present human trials that suggest only peripheral toxicity and conclude that there is no central action to be seen. And there are many who state that there are no effects at all, either inside or outside the CNS. The psychopharmacological status of bufotenine, like that of Uri Geller, may be essentially unanswerable.

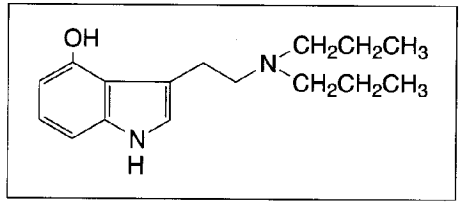
Two recent publications provide new and provocative input to this dialogue. One of these involved a series of appearances of a reddish substance on the East Coast called Chinese Love Stone, Black Stone, Rock Hard or Stud 100, being sold as aphrodisiacs. They were to be moistened and rubbed on the genitals, but as might be expected, quite a few were eaten and eventually smoked. They contained steroidal toxins, and were possibly related to some frog origins, but they were claimed to be bufotenine and indeed contained bufotenine in addition to several cardiotoxins as well as 5-MeO-DMT.

A second report carries, at least for me, much more impact. A study of the use of the seeds of a South American legume, *Anadenanthera columbrina* var. Cebil by the Argentine Shamans in Chaco Central, shows them to be dramatically psychedelic. And yet, extremely sophisticated spectroscopic analysis has shown them to contain bufotenine and only bufotenine as their alkaloid component.

The bottom line: I do not really know if bufotenine is a psychedelic drug. Maybe yes and maybe no.

#20. 4-HO-DPT; TRYPTAMINE, N,N-DIPROPYL-4-HYDROXY; 4-INDOLOL, 3-[2-(DIPROPYLAMINO)ETHYL]; N,N-DIPROPYL-4-HYDROXYAMINOTRYPTAMINE; 3-[2-(DIPROPYLAMINO)ETHYL]-4-INDOLOL

SYNTHESIS: A solution of 0.50 g 4-acetoxyindole (see under 4-HO-DET for its preparation) in 5 mL Et_2O was stirred and cooled to 0 °C with protection from atmospheric moisture. There was then added 0.5 mL oxalyl chloride. The reaction mixture was stirred for an additional 30 min, and the intermediate indoleglyoxyl chloride separated as a yellow crystalline solid but was not purified. This was treated with a 40% solution of dipropyl amine in anhydrous Et_2O, dropwise, until the pH was 8-9. The reaction was diluted with 100 mL $CHCl_3$ and shaken with 30 mL of a 5% aqueous $NaHSO_4$ followed by 30 mL of a saturated aqueous $NaHCO_3$ solution. After drying over anhydrous $MgSO_4$, the organic solvents were removed under vacuum. The residue was recrystallized from Et_2O/cyclohexane to give 0.73 g (78%) of 4-acetoxyindol-3-yl-N,N-dipropylglyoxylamide with a mp 130-131 °C. Anal: C,H,N.



To a stirred suspension of 0.50 g LAH in 10 mL anhydrous THF, stirred, under nitrogen and at room temperature, there was added a solution of 0.66 g 4-acetoxyindol-3-yl-N,N-dipropylglyoxylamide in 10 mL anhydrous THF. This was added dropwise at a rate that maintained the reaction at reflux. When the addition was complete, the reflux was maintained for an additional 15 min and then the reaction was cooled to 40 °C. The excess hydride and the product complex were destroyed by the addition of 1 mL EtOAc followed by 3 mL H_2O. The solids were removed by filtration, the filter cake washed with THF, the filtrate and washings pooled, and the solvents removed under vacuum. The residue was distilled at the KugelRohr and the distillate recrystallized from EtOAC/hexane. Thus there was obtained 0.27 g (51%) of N,N-dipropyl-4-hydroxytryptamine (4-HO-DPT) with a mp 96-97 °C. Anal: C,H,N.

DOSAGE: unknown

DURATION: unknown

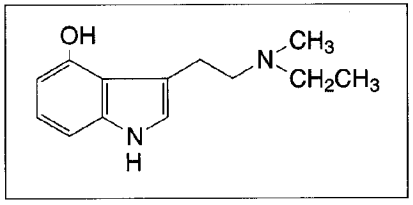
QUALITATIVE COMMENTS: (with 20 mg, orally) "Possible threshold, nothing more."

EXTENSIONS AND COMMENTARY: Here is another case where there just aren't enough observations to determine at what level the activity will be seen, or

what form it will take. The track record is pretty well established with the oxygen-free analogue DPT, and it would be hard to imagine a loss of potency by incorporating the "psilocin signature," the 4-hydroxy group. This threshold suggests something is nearby. It is a shame that the compound is rather difficult to make.

#21. 4-HO-MET; TRYPTAMINE, N-ETHYL-4-HYDROXY-N-METHYL; 4-INDOLOL, 3-[2-(ETHYLMETHYLAMINO)ETHYL]; N-ETHYL-4-HYDROXY-N-METHYLTRYPTAMINE; 3-[2-(ETHYLMETHYLAMINO)-ETHYL]-4-INDOLOL

SYNTHESIS: A solution of 0.50 g 4-acetoxyindole (see under 4-HO-DET for its preparation) in 5 mL Et_2O was stirred and cooled to 0 °C with protection from atmospheric moisture. There was then added 0.5 mL oxalyl chloride. The reaction mixture was stirred for an additional 30 min, and the yellow crystalline solid was removed by filtration and dissolved in 10 mL of anhydrous THF. This was treated with a 40% solution of methylethyl amine in anhydrous Et_2O, dropwise, until the pH was >10. The solvents were removed under vacuum and the residue dissolved in 200 mL $CHCl_3$. This was washed first with 50 mL 0.1 N HCl and then with 50 mL of saturated aqueous NaCl. After drying with anhydrous $MgSO_4$ and filtration, the solvent was removed under vacuum. The residue was recrystallized from Et_2O to give 0.60 g (yield 73%) of 4-acetoxyindol-3-yl-N-ethyl-N-methylglyoxylamide with a mp 179-180 °C. Anal: C,H,N.



To 10 mL of a stirred solution of LAH (1 M in THF under N_2), there was added dropwise a solution of 0.57 4-acetoxyindol-3-yl-N-ethyl-N-methylglyoxylamide in 10 mL anhydrous THF. When the addition was complete, the reaction mixture was brought to a reflux for 15 min. After cooling to 40 °C, sufficient water was added to decompose both the reaction complex and the excess hydride. After filtration through Celite (under an N_2 atmosphere), the solvent was removed under vacuum, and the solid residue recrystallized from EtOAc/hexane to provide 0.18 g (41%) N-ethyl-4-hydroxy-N-methylindole (4-HO-MET) with a mp 118-119 °C. Anal: C,H,N.

DOSAGE: 10 - 20 mg, orally

DURATION: 4 - 6 h

QUALITATIVE COMMENTS: (with 20 mg, orally) "Qualitatively a lot like

psilocin. It started within the first half-hour, and at the max, I felt the same alteration of color and form, and at times, sound was felt. As with psilocin, the experience was wave-like, with an alteration of effects between near-normal perception at one minute, only to be swept up in a swirl of altered concepts the next minute."

EXTENSIONS AND COMMENTARY: First, an apology for just a single entry in the comments section. This, and several other of these substituted hydroxy and methoxy tryptamines, had had earlier evaluations, but the notes are not at hand and cannot be used. Much will have to come back from memory, and there must be an appropriate fuzziness allowed for the concluded generalization as to dose and duration. With this particular compound, some of the original observations suggested that it was more potent than psilocin, certainly more dramatic. But at the bottom line, I doubt that this ethyl homologue, or the isopropyl homologue 4-HO-DIPT for that matter, could be distinguished from the methyl counterpart psilocin in any blind clinical study.

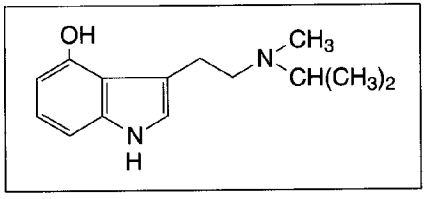
What's to choose between them? From the viewpoint of synthesis, the cost and availability of the secondary amine will certainly be a factor. Both methylethyl amine and methylisopropylamine are available, but are quite expensive. Dimethylamine, on the other hand, is dirt cheap but it is a recognized precursor to DMT and thus is difficult to find. In any event, the dimethyl compound is widely available in the mycological arena, and I suspect it would be simplest to stay with nature.

#22. 4-HO-MIPT; TRYPTAMINE, 4-HYDROXY-N-ISOPROPYL-N-METHYL; 4-INDOLOL, 3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]; 4-HYDROXY-N-ISOPROPYL-N-METHYLTRYPTAMINE; 3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]-4-INDOLOL

SYNTHESIS: A solution of 0.50 g 4-acetoxyindole (see under 4-HO-DET for its preparation) in 5 mL Et_2O was stirred and cooled to 0 °C with protection from atmospheric moisture. There was then added 0.5 mL oxalyl chloride. The reaction mixture was stirred for an additional 30 min, and the yellow crystalline solid was removed by filtration and dissolved in 10 mL of anhydrous THF. This was treated with a 40% solution of methyl isopropylamine in dry Et_2O, dropwise, until the pH of the reaction mixture was >10. The solvents were removed under vacuum and the residue dissolved in 200 mL $CHCl_3$. This was washed first with 50 mL 0.1 N HCl and then with 50 mL of saturated aqueous NaCl. After drying with anhydrous $MgSO_4$ and filtration, the solvent was removed under vacuum. The residue was recrystallized from $CHCl_3$/hexane to give 0.68 g 4-acetoxyindol-3-yl-N-isopropyl-N-methylglyoxylamide with a mp 211-212 °C (79%).

To 10 mL of a stirred solution of LAH (1 M in THF under N_2), there was

added, dropwise, a solution of 0.60 mg 4-acetoxyindol-3-yl-N-isopropyl-N-methylglyoxylamide in 10 mL anhydrous THF. When the addition was complete, the reaction mixture was brought to a reflux on the steam bath for 15 min. After cooling to 40 °C, sufficient water was added to decompose both the reaction complex and the excess hydride. After filtration through Celite (under an N_2 atmosphere), the solvent was removed under vacuum, and the solid residue recrystallized from EtOAc/hexane. There was thus obtained . 34 g (74%) of 4-hydroxy-N-methyl-N-isopropyltryptamine (4-OH-MIPT) with a mp of 123-124 °C. 4-HO-MIPT discolors quickly if it is not kept in an inert atmosphere and in a freezer. Anal: C,H,N.



DOSAGE: 12 - 25 mg, orally (as the indolol or the acetate)

DURATION: 4 - 6 h

QUALITATIVE COMMENTS: (with 9 mg, orally) "I am stuck just part way on. There is some retinal activity with my eyes closed. Maybe I am a little light-headed, a little starry. Nothing much."

(with 12 mg, orally) "It was just an hour ago that I swallowed the capsule, and everything is happening. It was completely developed at 45 minutes. The imagery with my eyes closed is vivid. The music is exceptionally sensual. I notice a tendency to twitch but it doesn't bother me. Everything is rolling — how can they allow an erotic piece like the Saint-Saëns second piano concerto to ever appear in public, let alone over the radio? A very rapid decline between the third and fourth hour. A rich day for love, insights, fantasy, and for retreating into one's mind. A rich day for discovery."

(with 12 mg, orally) "I suspended the solids in water, and a drop of HCl put it into solution immediately. The first awareness was unmistakable at twenty minutes, and from there it was a rapid and noisy development ending at about an hour. But this lasted for only another 40 minutes, and then dropped off quite rapidly. The erotic was excellent, but there were few visuals and I had difficulty connecting fantasy to music. Good appetite afterwards, and I had no trouble getting to sleep."

(with 15 mg acetate ester, orally) "An interesting mixture of intoxication and sedation, progressing to a very relaxed state with some motor incoordination. Just a little bit like alcohol. There was no drifting of thoughts nor any gut disturbance at any time, although I wasn't very hungry. Conversation was easy."

(with 20 mg, orally) "Early signs (muscle sensations) were noticed in 10 minutes. In another 10 minutes a rapid heightening of all senses ensued, reaching a plateau in 40 minutes and beginning to decline in 3 hours with a return to near normal in 5-6 hours. The intensity of the experience is marked. At the plateau, communication (verbal) is difficult with intense alteration in the sense of time and distance. Multiple and overlapping wave forms occur with an extremely intense color alteration. Drifting in and out of the body is common with an increased sense of body processes, i.e., blood flow in vessels. Muscular sense is increased and a feeling of soaring in bodiless flight is experienced. A mild vertigo was felt with attempted walking but is not associated with nausea. Some anxiety was experienced initially, but could be interpreted as a reaction to the extremely powerful onset. A curious, probably idiosyncratic effect, was of possessing the essence of sexual power associated with being a large jungle cat. The idea was prominent for some time. Conservatively, this compound is at least twice as active as psilocin at comparable doses, in terms of plateau or peak effect. External stimuli, especially light, were distracting to the point of annoyance. Sounds can be seen, words explode into showers of bright points with eyes closed. Other eyes-closed imagery is prominent with patterns (in color); at times soaring clouds dominate the eyes-closed scenery. I cannot overemphasize the intensity of the experience. I would not want to go much higher than 20 milligrams (50 milligrams of psilocin is not as intense)."

(with 30 mg acetate ester, orally) "It was as if I had downed a few martinis in a hurry — except that there were eyes-closed visuals in a lot of different colors, especially metallic greens. I had jaw clenching and a body tremor, reminding me of ecstasy except it was not in any way stimulating. I listened to music in front of a fireplace in a darkened room and I saw bright, colorful, unstructured patterns. Seven hours and I fell into an easy sleep and was fine the next day."

EXTENSIONS AND COMMENTARY: This is a two-carbon homologue of psilocin and, as the latter chemical is orally active, it is not surprising that this is, as well. One direct comparison between the two materials, on widely separated days and at very high levels, indicated that 20 milligrams of 4-HO-MIPT was fully equivalent to 50 milligrams of psilocin, in one report. And yet, in another report with 30 milligrams of the acetate ester, things were considerably more modest. At these higher levels, the onset was noted well within the first half hour.

Here, as with the 4-HO-DMT (psilocin) and the 4-HO-DET entries, some care must be made with the use of the term "acetate" or "phosphate." As these materials are both bases (tertiary amines) and acids (hydroxy indoles), they are, in effect, internal salts. For stability, they are usually converted into salts (at the amine end) or esters (at the phenolic end), or both. In this context, the term "acetate" can mean either modification, a salt or an ester involving acetic acid. And, of course, a phosphate can be either a salt or an ester. I will try to append the additional term "salt" or "ester" whenever this ambiguity is possible. In all of these studies, the acetate is the ester, and some of these are free bases, some are the hydrochloride salts and some are the fumarate salts.

A large number of related homologues of psilocin have been synthesized and described, and some of them tasted to varying degrees, but none of them to a degree of definition to justify a recipe devoted just to them. With the 4-hydroxyl

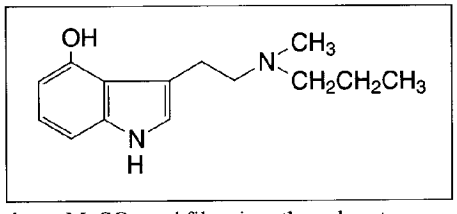
group assuring some measure of oral activity, all of these could serve as a structural activity relationship gestalt to selectively, and specifically, evaluate the geometric nature of the nitrogen substituents.

If one were to be a complete perfectionist in these areas of chemistry, one should actually make the phosphate ester of 4-HO-MIPT, as this would be the exact homologue of psilocybin. But that would be a great amount of additional work, just to have the body chop off the ester group as soon as it had the chance. The current thinking is that there would be the same activity with either compound, making allowances for the change in molecular weight. But at least it might be a lot more stable for storage. What about the sulfate ester? It should be a very stable salt, and the body has sulfatases just as it has phosphatases. Maybe the ubiquitous non-specific esterases would work as well. A number of studies have been made with the acetate ester (some mentioned here) and it should whap off immediately once it's inside you.

A careful clinical comparison of the acetate ester of psilocin with the phosphate ester and the free phenol might help resolve this question. The ideal way of resolving this would be to run pharmacokinetic studies on blood levels of these three materials, in parallel with studies of the psychopharmacological responses. I feel that this is not likely to be done in the foreseeable future.

#23. 4-HO-MPT; TRYPTAMINE, 4-HYDROXY-N-METHYL-N-PROPYL; 4-INDOLOL, 3-[2-(METHYLPROPYLAMINO)ETHYL]; 4-HYDROXY-N-METHYL-N-PROPYLTRYPTAMINE; 3-[2-(METHYLPROPYLAMINO)ETHYL]-4-INDOLOL

SYNTHESIS: A solution of 0.50 g 4-acetoxyindole (see under 4-HO-DET for its preparation) in 5 mL Et_2O was stirred and cooled to 0 °C with protection from atmospheric moisture. There was then added 0.5 mL oxalyl chloride. The reaction mixture was stirred for an additional 30 min, and the yellow crystalline solid was removed by filtration and dissolved in 10 mL of anhydrous THF. This was treated with a 40% solution of methylpropyl amine in anhydrous Et_2O, dropwise, until the pH was >10. The solvents were removed under vacuum and the residue dissolved in 200 mL $CHCl_3$. This was washed first with 50 mL 0.1 N HCl and then with 50 mL of saturated aqueous NaCl. After drying with anhydrous $MgSO_4$ and filtration, the solvent was removed under vacuum. The residue was recrystallized from EtOAc/hexane to give 0.54 g (63%) of 4-acetoxyindol-3-yl-N-methyl-N-propylglyoxylamide with a mp 94-95 °C. Anal: C,H,N.



To 8 mL of a stirred solution of LAH (1 M in THF under N_2), there was added, dropwise, a solution of 0.48 4-acetoxyindol-3-yl-N-methyl-N-propylglyoxylamide in 8 mL anhydrous THF. When the addition was complete, the reaction mixture was brought to a reflux for 15 min. After cooling to 40 °C, sufficient water was added to decompose both the reaction complex and the excess hydride. After filtration through Celite (under an N_2 atmosphere), the solvent was removed under vacuum, and the oily residue dissolved in MeOH, neutralized with HCl, and Et_2O added until crystallization started. Thus there was obtained 0.23 g (54% of theory) 4-hydroxy-N-methyl-N-propylindole hydrochloride (4-HO-MPT) with a mp 162-163 °C. Anal: C,H,N.

DOSAGE: unknown

DURATION: unknown

QUALITATIVE COMMENTS: (with 8 mg, orally) "There is a very mild visual distortion, and a prominent vertigo without nausea. In the second hour there is still some enhancement of visual detail, but I am not endowed with the flight of ideas or philosophical concepts as with psilocin. I am rapidly subsiding and I am able to eat normally. Residual insomnia lasted eight hours."

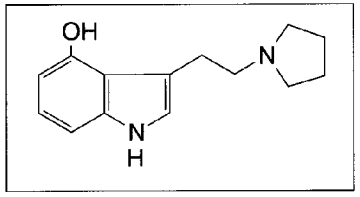
EXTENSIONS AND COMMENTARY: As with the discussion presented with the lower homologue, 4-HO-DET, there is not enough here to give a fair estimate of either dose or duration. In my file under this compound I can find only this one report. Extrapolation suggests that this might be yet another material active in the psilocin range of somewhere up to 20 milligrams, all orally. Maybe it is a generality that anything with up to six carbons attached one way or another to the tryptamine nitrogen atom (and all sporting a 4-hydroxy group, of course) will be active in the 10 to 20 milligram range. This certainly holds for the methyl-methyl, methyl-ethyl, methyl-propyl, methyl-isopropyl, diethyl, dipropyl and diisopropyl. That makes it a pretty good generalization.

How far can this argument be pushed? What about one of the N-alkyl groups having four carbons? Keeping the other N-alkyl group as the smallest and most simple methyl group, all four isomeric compounds are known. There is the n-butyl isomer (4-HO-MBT, an oil), the isobutyl isomer (4-HO-MIBT, mp 142-145 °C), the secondary butyl isomer (4-HO-MSBT, mp 138-140 °C) and the tertiary butyl isomer (4-HO-MTBT, mp 225-226 °C). Of these four materials only 4-HO-MTBT has been looked at as a possible psychedelic. Some 15 milligrams produced virtually no effects, maybe a hint of something in a few minutes and then nothing. Probably pure placebo response.

Many yet heavier substitution patterns are in the literature but they, too, are unexplored. The symmetrical disubstituted isomers are listed separately in these recipes.

#24. 4-HO-pyr-T; TRYPTAMINE,4-HYDROXY-N,N-TETRAMETHYLENE; 4-INDOLOL,3-[2-(1-PYRROLIDYL)ETHYL]; PYRROLIDINE, 1-[2-[3-(4-HYDROXY)INDOLYL]ETHYL]; 4-HYDROXY-N,N-TETRAMETHYLENETRYPTAMINE; 3-[2-(1-PYRROLIDYL)ETHYL]-4-INDOLOL; 1-[2-[3-(4-HYDROXY)INDOLYL]ETHYL]PYRROLIDINE; "4-HYDROXYPYRROLIDYLTRYPTAMINE"

SYNTHESIS: A solution of 0.50 g 4-acetoxyindole (see under 4-HO-DET for its preparation) in 5 mL Et_2O was stirred and cooled to 0 °C with protection from atmospheric moisture. There was then added 0.5 mL oxalyl chloride. The reaction mixture was stirred for an additional 30 min, and the intermediate indoleglyoxyl chloride separated as a yellow crystalline solid but was not purified. This was treated with a 40% solution of pyrrolidine in anhydrous Et_2O, dropwise, until the pH was 8-9. The reaction was diluted with 100 mL $CHCl_3$ and shaken with 30 mL of a 5% aqueous $NaHSO_4$ followed by 30 mL of a saturated aqueous $NaHCO_3$ solution. After drying over anhydrous $MgSO_4$, the organic solvents were removed under vacuum. The residue was recrystallized from $CHCl_3$/hexane to give 0.47 g (55%) of 4-acetoxyindol-3-yl-N,N-tetramethyleneglyoxylamide with a mp 174-176 °C. Anal: C,H,N.



To a stirred suspension of 0.25 g LAH in 10 mL anhydrous THF, under nitrogen and at room temperature, there was added a solution of 0.30 g 4-acetoxyindol-3-yl-N,N-tetramethyleneglyoxylamide in 10 mL anhydrous THF. This was added, dropwise, at a rate that maintained the reaction at reflux. When the addition was complete, the reflux was maintained for an additional 15 min and then the reaction was cooled to 40 °C. The excess hydride and the product complex were destroyed by the addition of 0.5 mL EtOAc followed by 1.5 mL H_2O. The solids were removed by filtration, the filter cake washed with THF, the filtrate and washings pooled, and the solvents removed under vacuum. The residue was recrystallized from EtOAc/hexane to give 0.12 g (50%) of 4-hydroxy-N,N-tetramethylenetryptamine (4-HO-pyr-T) with a mp 193-195 °C. Anal: C,H,N.

DOSAGE: >20 mg

DURATION: unknown

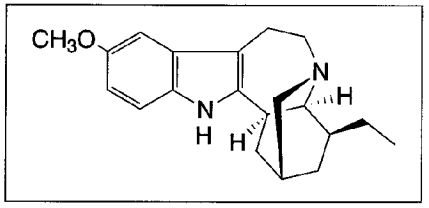
QUALITATIVE COMMENTS: (with 20 mg, orally) "This substance proved to be quite unlike psilocin and bordered on the bizarre. There was a latency period of about three hours after ingestion before the onset was noted. Visual disturbances were minimal; no alteration in colors or objects occurred. The nature of this compound was characterized by the heightening of the intellectual process, but not

to the extent seen with psilocin. The entire experience was more 'stimulant-like' rather than hallucinogenic. A very unpleasant ride. Have no desire to go deeper or, indeed, to look at the other cyclic analogues."

EXTENSIONS AND COMMENTARY: There are three pyrrolidine amines in this tryptamine compilation, and all three are simply weird and illogical. Both the simple "pyrrolidyl tryptamine" (pyr-T) and the 5-methoxy counterpart (5-MeO-pyr-T) caused physical distress, and this one (4-HO-pyr-T) seems to be more of a stimulant than a psychedelic. In all three cases (and with the 5,6-methylenedioxy example as well) the other two-ring systems that often accompany the pyrrolide example as a "set" were simply not explored. This is due, largely, to the unexpected and generally negative responses to the pyrrolidine archetype. The piperidine homologue (4-HO-pip-T) is a white crystalline solid with a mp of 180-181 °C. The morpholine analogue (4-HO-mor-T) is also a white crystalline solid with a mp of 177-178 °C.

#25. IBOGAINE; 12-METHOXYIBOGAMINE

SYNTHESIS: There have been three total syntheses of ibogaine reported in the chemical literature. The first of these was a thirteen-step process published about 30 years ago. The chemistry lab can serve a fine function for both isolation and purification of ibogaine from plant sources, but in the real world, there is no practical way to start from a bottle of nicotinic acid and actually prepare useful amounts. The parent ring system contains two chiral centers, neither of which is amenable to easy manipulation. Because of these two separate and largely inaccessible chiral centers there are, in theory, four distinct isomers of ibogaine which are difficult to resolve. When the term "synthetic" is used in regard to ibogaine in the scientific journals, it usually applies to the resynthesis of the parent alkaloid from the demethylated metabolite. For reference purposes, here are the fingerprint numbers from the infrared spectra: for the free base: IR (in cm^{-1}): 741, 799, 830, 1037, 1111, 1148; mp 152-153 °C. For the hydrochloride salt: IR (in cm^{-1}): 638, 810, 832, 925, 1031, 1149; mp 299-300 °C (dec).



DOSAGE: (from hundreds of milligrams up to a gram or more, orally)

DURATION: (quite long)

EXTENSIONS AND COMMENTARY: Here is an example of a most remarkable material that has allowed people to have some rather complex and dramatic experiences. Any effort to present a fair overview of its action, through a selection of individual responses in the "extension and commentary" format would fail, as it would ignore the impact of the set and setting on the subject. Here I will mention a few of these different sets, and a leading author who gives more detail.

There is a well studied history of the use of the iboga plant in the religious rituals in Gabon and its neighboring countries, from the early part of the 19th century. The Buiti religion calls for the use of the root bark of *Tabernanthe iboga* as a sacrament, and the reports of its psychopharmacological effectiveness reflect these needs (see Samorini).

Another area of reports that can be called upon reflects the exploration of the isolate from this plant, or the isolated active component ibogaine itself, in the study of its use with psychotherapy. Here the reports reflect the physician/patient interaction with an emphasis on early memory and the reliving of past experiences (see Naranjo). In clinical studies such as these, a typical dose would be four hundred milligrams of the chemical, twice this weight of the crude isolate, and perhaps ten times this weight again if the actual root bark is used.

Yet another source of reports is to be found in some studies that are exploring ibogaine as a treatment for heroin dependency (see De Rienzo and Beal). This end-goal of retrieving evidence of addiction confrontation and addiction control can certainly color any published reports in its own way. Here, it is only the chemical ibogaine that is used, and typical dosages are at or above 1000 milligrams.

There is no question but that ibogaine is a rough trip, physically as well as mentally. Here is one report that shows the body aspects of its use.

(with 200 mg, orally) "Subjectively, the most unpleasant symptoms were the anxiety, the extreme apprehension, and the unfamiliar mood associated with visual and bodily hallucinations. The visual hallucinations appeared only in the dark and consisted of blue disks dancing up and down the walls. Dysesthesia of the extremities, a feeling of light-weightedness, and hyperacusis were other symptoms noted. Autonomic signs, such as dryness of the mouth, increased perspiration, slight pupillary dilation, and increase in pulse rate, as well as extrapyramidal syndromes (fine tremors, slight ataxia, enhanced tendon reflexes and clonus) were also present. The peak effect was reached at about 2 hours after swallowing the drug; it subsided gradually, leaving as a residue complete insomnia. No undesirable after-effects, such as exhaustion or depression occurred."

As was pointed out in a pharmacological review (see Popik et al.), as the hallucinogenic dose appears to be several times higher than the stimulant dose, the user must endure intense and unpleasant central stimulation in order to experience the hallucinogenic effects.

But as fascinating as the pharmacology of ibogaine, it is the chemistry of this alkaloid that is overwhelmingly awesome. The presence of four isomers was

mentioned in the chemistry section above, but this fact was not appreciated until the 1960's and even then, a couple of troublesome errors were made that confused the absolute configuration picture quite badly. The story has been accurately told in a (nearly) hundred page review chapter (see Cordell) which is a must for anyone who wants to risk understanding some pretty far-out chemistry. Oh my, there are a lot of closely related alkaloids. As to indolic alkaloids in general, there are well over two thousand of them, with a few dozen added every year. And most of these are kosher tryptamines in that they carry the tryptamine structural skeleton. And, in turn, a great number of the tryptamine alkaloids are found in the remarkable family Apocynaceae, which is the ultimate treasure-trove of alkaloids, probably the richest single source of pharmacologically active compounds in the entire plant kingdom. It is made up, largely, of tropical shrubs of the dogbane group, which almost always ooze out a sticky sap when you break off a twig. They have showy flowers, and the reputation of being very poisonous.

And this all leads smoothly to the botany, which is almost as convoluted as the chemistry. Here, let me list the plants that contain ibogaine, or that should contain it. Allow me a brief run-down of binomials. There is a number of species that are, or have been, classified as belonging to the *Tabernanthe* genus and which are reasonable sources of ibogaine, and which are logical alternatives, psychopharmacologically, to the iboga plant itself.

Tabernanthe iboga. This is the major source of ibogaine and is found in Gabon, mentioned above.

Tabernanthe orientalis. This plant is now called *Ervatamia orientalis*, and is found in Western Australia. The leaves contain ibogaine, along with six minor alkaloids that are closely related, structurally.

Tabernanthe pubescens. This is found in Zaire, and contains a number of alkaloids closely related to ibogaine in structure, as well as ibogaine itself.

Tabernaemontana spp. This genus is from a tribe within the family Apocynaceae that is called the Tabernaemontaneae. As an official sub-family it would be called Tabernaemontanoideae. It is because of the casual use of names such as these that botanical binomialists are rarely invited to social functions. It (this Genus, that is) contains several dozen species, some with ibogaine, many with analgesic or sedative action in experimental animals, and some with quite a history of native usage either in Africa or Southeast Asia.

And there are many plants in the Apocynaceae family that carry fascinat-

ing alkaloids that are closely related in structure to ibogaine and which, potentially, might have a similar psychopharmacology. In most of these, ibogaine is present in very small amounts, if at all.

Anacampta spp. have usually been published as *Tabernaemontana* spp., as have been species originally published as part of the Genera *Bonafousia, Capuronetta* (which has become the species *capuronni* under this Genus), *Conopharyngia, Ervatamia, Gabunia, Hazunta, Muntafara, Pagiantha, Pandaca, Peschiera, Phrissocarpus,* and *Stenosolen.* All of these contain alkaloids related to Ibogaine.

Callichilia barteri has appeared as *Hedranthera barteri,* but *C. subsessilis* demands the name *Tabernaemontaneae subsessilis* in the presentation of its alkaloid content.

Creoceras, Rejoua, Schzozygia, Stemmadenia and *Voacanga* have, with all their species, remained intact with their original names.

Peschiera echinata, this is one of some ten species within the Tabernaemontaneae classification, with some 2% alkaloid content in its leaves. Ibogaine is present.

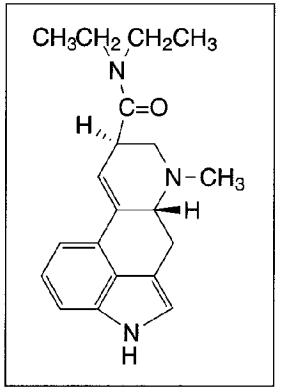
Voacanga schweinfurthii var. *puberula* (known in the older literature as *Voacanga puberula*) contains some ten related alkaloids. The major one, found in the seeds, and is tabersonine, is present at a rather remarkable 3.5%. Ibogaine is present in the root bark but, at a concentration of 200 mg/Kg (0.02%), it is truly a minor constituent.

#26. LSD-25; ACID; LYSERGIDE; D-LYSERGIC ACID DIETHYLAMIDE; METH-LAD; D-LYSERGAMIDE, N,N-DIETHYL; N,N-DIETHYL-D-LYSERGAMIDE; 9,10-DIDEHYDRO-N,N-DIETHYL-6-METHYLERGOLINE-8β-CARBOXAMIDE

SYNTHESIS: A solution of 6.7 g KOH in 100 mL H_2O, under an inert atmosphere and magnetically stirred, was brought to 75 °C, and 10 g ergotamine tartrate (ET) added. The reaction mixture turned yellow as the ergotamine went into solution over the course of 1 h. The stirring was continued for an additional 3 h. The reaction mixture was cooled to about 10 °C with an external ice bath, and acidified to a pH of about 3.0 by dropwise addition of 2.5 N H_2SO_4. White solids began to appear early in the neutralization; approximately 60 mL of sulfuric acid was required. The reaction mixture was cooled overnight, the solids removed by filtration, and the filter cake washed with 10 mL Et_2O. The dry solids were transferred to a beaker, suspended in 50 mL 15% ammonia in anhydrous ethanol, stirred for 1 h, and separated by decantation. This extraction was repeated, and the original decantation

and the second extract combined and filtered to remove a few hundred milligrams of unwanted solids. The clear filtrate was stripped of solvent under vacuum, the residual solids dissolved in 50 mL of 1% aqueous ammonia, and this solution was acidified as before with 2.5 N H_2SO_4. The precipitated solids were removed by filtration and washed with Et_2O until free of color. After drying under vacuum to a constant weight, there was obtained 3.5 g of d-lysergic acid hydrate, which should be stored in a dark, sealed container.

A suspension of 3.15 g d-lysergic acid hydrate and 7.1 g of diethylamine in 150 mL $CHCl_3$ was brought to reflux with stirring. With the external heating removed, there was added 3.4 g $POCl_3$ over the course of 2 min, at a rate sufficient to maintain refluxing conditions. The mixture was held at reflux for an additional 5 min, at which point everything had gone into solution. After returning to room temperature, the solution was added to 200 mL of 1 N NH_4OH. The phases were separated, the organic phase dried over anhydrous $MgSO_4$, filtered, and the solvent removed under vacuum. The residue was chromatographed over alumina with elution employing a 3:1 C_6H_6/$CHCl_3$ mixture, and the collected fraction stripped of solvent under hard vacuum to a constant weight. This free-base solid can be recrystallized from benzene to give white crystals with a melting point of 87-92 °C. IR (in cm^{-1}): 750, 776, 850, 937 and 996, with the carbonyl at 1631. The mass spectrum of the free base has a strong parent peak at mass 323, with sizable fragments at masses of 181, 196, 207 and 221.



This base was dissolved in warm, dry MeOH, using 4 mL per g of product. There was then added dry d-tartaric acid (0.232 g per g of LSD base), and the clear, warm solution treated with Et_2O, dropwise, until the cloudiness did not dispel on continued stirring. This opaqueness set to a fine crystalline suspension (this is achieved more quickly with seeding) and the solution was allowed to crystallize overnight in the refrigerator. Ambient light should be severely restricted during these procedures. The product was removed by filtration, washed sparingly with cold MeOH, with a cold 1:1 MeOH/Et_2O mixture, and then dried to constant weight. The white crystalline product was lysergic acid diethylamide tartrate with two molecules of MeOH of crystallization, with a mp of about 200 °C with decomposition, and weighed 3.11 g (66%). Repeated recrystallizations from MeOH produced a product that became progressively less soluble, and eventually virtually insoluble, as the purity increased. A totally pure salt, when dry and when shaken in the dark, will emit small flashes of white light.

DOSAGE: 60 to 200 micrograms, orally

DURATION: 8 to 12 h

QUALITATIVE COMMENTS: In the case of LSD, it seems presumptuous to attempt to select typical comments for quotation. Literally thousands of reports are in the literature, from early exploratory research, to clinical applications for treatment of autism, of alcoholism, or mental illness, to assisting in psychotherapy and in the dying process, to the adventures of the military in both intelligence and chemical warfare, to innumerable anecdotal tales of pleasure and pain. Dozens of books have been devoted to these topics.

EXTENSIONS AND COMMENTARY: LSD is an unusually fragile molecule and some comments are in order as to its stability and storage. As a salt, in water, cold, and free from air and light exposure, it is stable indefinitely. There are two sensitive aspects of its structure. The position of the carboxamide attachment, the 8-position, is affected by basic, or high pH, conditions. Through a process called epimerization, this position can scramble, producing isolysergic acid diethylamide, or iso-LSD. This product is biologically inactive, and represents a loss of a proportionate amount of active product. A second and separate point of instability is the double bond that lies between this 8-position and the aromatic ring. Water or alcohol can add to this site, especially in the presence of light (sunlight with its ultraviolet energy is notoriously bad) to form a product that has been called lumi-LSD, which is totally inactive in man. Oh yes, and often overlooked, there may be only an infinitesimal amount of chlorine in treated tap water, but then there is only an infinitesimal amount of LSD in a typical LSD solution. And since chlorine will destroy LSD on contact, the dissolving of LSD in tap water is not appropriate.

There are many synthetic methods developed and reported for the preparation of LSD. All of them start with lysergic acid, and for that reason it has been listed as a Schedule III controlled drug, as a depressant, under Federal law. The amide lysergamide, a component of several varieties of morning glory seed, is also a controlled drug and, by law, a depressant. The earliest syntheses of LSD involved the use of an azide intermediate (the original Hofmann process, 1955), mixed anhydrides with trifluoroacetic anhydride (1956) or sulfuric anhydride (SO_3-DMF on the lithium salt, 1959), with the peptide condensation agent N,N'-carbonyldiimidazole (1960), or with the acid chloride as the active intermediate with $POCl_3$, PCl_5 or thionyl chloride (1963) or just phosphorus oxychloride (1973). Most methods are faulted due to excessive moisture sensitivity, generation of side-products, or epimerization or inversion at the 8-position carbon to form d-iso-LSD. The $POCl_3$ procedure is clean and fast, and is the preferred process today for the synthesis of a wide variety of substituted lysergamides.

The term "LSD" comes from the initials of the German for lysergic acid diethylamide, or LyserSäure Diäthylamid. The number "25" following it has many myths attached to it, such as: it was the 25th form of LSD that Hofmann tried, or it was his 25th attempt to make LSD. From my own experience with chemical companies that are allied with pharmaceutical houses, I had assumed that the chemical name (which might be a mouthful for the pharmacologist) was simply replaced with a pronounceable code number equivalent. But the answer here is yet simpler. Hofmann, in his *LSD, My Problem Child* wrote: "In 1938, I produced the twenty fifth substance in a series of lysergic acid derivatives: lysergic acid diethylamide, abbreviated LSD-25 ... for laboratory usage."

Within a few years of the discovery of the extraordinary potency of LSD, a large number of close analogues were synthesized by Hofmann and his allies at Sandoz. Over the following decade many were tested in humans, both in patients and healthy subjects, with the qualitative descriptions and dosages published in the medical literature.

A number of analogues of LSD have maintained the diethylamide group unchanged, but additions or changes have been made in the pyrrole ring.

--- indole-ring substituent ---		
at N-1	at C-2	code
-H	-H	LSD-25
$-COCH_3$	-H	ALD-52
$-CH_3$	-H	MLD-41
$-CH_2OH$	-H	
$-CH_2N(CH_3)_2$	-H	
-H	-Br	BOL-148
-H	-I	
$-CH_3$	-Br	MBL-61
$-CH_3$	-I	MIL

ALD-52. 1-Acetyl-N,N-diethyllysergamide. This material has been explored in the 50-175 microgram range and there are a number of human trials reported, with varying conclusions. One found that there was less visual distortion than with LSD and it seems to produce less anxiety and was somewhat less potent than LSD. Another report claimed it was more effective in increasing blood pressure. Yet another could not tell them apart. ALD-52 just may have been the drug that was sold as "Orange Sunshine" during the "Summer of Love" in the late '60's. Or "Orange Sunshine" may have been, really, LSD. This was the focus of a fascinating trial where two defendants were accused of distributing LSD, whereas they claimed that it was ALD-52, which was not an illegal drug. The prosecution claimed that as it hydrolyses readily to LSD, for all intents and purposes, it was LSD, and anyway, you had to go through the illegal LSD to get to ALD-52 by any of the known chemical syntheses. The defendants were found guilty. And yet, I do not

know who has actually measured the speed or ease of that reaction. If ALD-52 hydrolyses so easily to LSD, and the body is indeed a hydrolytic instrument, then these two drugs should be absolutely equivalent in every particular. This is the ergot equivalent of the psilocybin to psilocin argument, except this is an acetamide rather than a phosphate ester.

MLD-41. 1-Methyl-N,N-diethyllysergamide. The 1-methyl homologue of LSD has more of a somatic than sensory effect, has fewer visuals, and is less well accepted than LSD, with the range of dosages being from 100 to 300 micrograms. This indicates that it is perhaps a third the potency of LSD, which is in accord with both pupilary dilation and reflex action. However, the cardiovascular responses are actually increased. Besides being less potent than LSD, it appears to have a slower onset but is equally long lived. There is cross-tolerance between MLD-41 and LSD.

BOL-148. 2-Bromo-N,N-diethyllysergamide. This synthetic ergot derivative, along with its 1-methyl homologue MBL-61 (mentioned below) should be used as powerful tools for studying the mechanism of action of LSD in the human animal. It does not have LSD-like effects in man. At 6 to 10 milligrams orally, there are some mental changes noted. But in another study, 20 milligrams a day was administered to a subject for 7 days, and there were no reported effects. And yet it is as potent a serotonin agonist as is LSD. How can serotonin be argued as a neurotransmitter that is a major player in explaining the action of psychedelic drugs, when this compound is nearly without activity?

There are some suggestions that an intravenous route may be more effective. I have heard of effects being noted at maybe a milligram and a short (2-3 hour) intoxication following 20 milligrams administered over a 20 minute period. I was involved many years ago in a study of radio-labelled BOL-148 which was made by the bromination of LSD. I was quite sure that the only radioactive material present was BOL-148, but there could well have been some unreacted LSD still present which would, of course, still be psychoactive. The synthesis is not clean — I was tempted to make an entry for this compound if only to reproduce Albert Hofmann's original published experimental procedure. He reacted 13.2 grams of N-bromosuccinimide (in 400 mL dioxane), with 1.2 liters of dioxane containing 25 grams of LSD. This gave 11 grams of crude product which had to be recrystallized. The radioactive synthesis used effectively elemental bromine, and gave yields of from 5 to 15%. Visualize that reaction! A warm flask containing over a quart of warm solvent in which there were maybe half a million doses of LSD.

1-Hydroxymethyl-LSD, 1-dimethylaminomethyl-LSD and 2-iodo-LSD. These three additional compounds are shown here because they were described in a synthetic flurry that followed the discovery of the activity of LSD. But at the moment I know neither their internal Sandoz codes nor if they had ever been explored in man. This is a kind of frustrating catch-all entry, in that the long index will send you here, and once here you realize that nothing is known. Well, at least the compounds are known, and perhaps there is something in the Sandoz vaults that might be interesting. I do not have access to them.

MBL-61. 2-Bromo-N,N-diethyl-1-methyllysergamide. This is the compound BOL-148 (mentioned above) with a methyl group attached to the 1-position of the indole ring (LSD has a hydrogen there). This would be an even more tantalizing challenge to the serotonin theory for central activity of the psychedelics, in that it is without any activity in man at an oral dose of 14 milligrams (similar to the inactivity of the BOL-61 compound, but it is some five times more potent as a serotonin agonist. With it, as with the iodinated analogue MIL, there are many examples of the compromising of scientific integrity in the quest for funds and recognition. Both compounds are as effective as LSD itself in displacing labelled LSD that is bound to the post-synaptic serotonin receptor sites in animal brains. But neither of them show any LSD-like activity. But both have been labelled with ^{11}C or ^{122}I to give positron emitting forms that can be administered to man and localized in a positron emission tomography instrument (a PET scanner).

I was at a meeting of a NIDA study section a few years ago, where someone presented some findings with a group of subjects who were complaining of continuing mental problems allegedly due to LSD exposure. A chart was put up showing the outline of the brain with the locations of the EEG foci that were observed in one of these subjects. Alongside it was a PET scan showing the distribution of radioactive LSD in a subject. The purpose was to discuss the similarities and differences of the coordinates of electrical activity and radioisotope concentration. I innocently asked what positron isotope had been used, as I did not know of any successful positron labelling of LSD. Carbon 11, I was told. Where in the molecule was the label incorporated, I asked. In the 1-position methyl group. It was finally acknowledged that the compound that had actually been used was 2-iodo-1-methyl-LSD, our MIL compound, which is quite a different world. A pharmacologist might say that they are similar in action (looking at serotonin, not psychedelic action), and a chemist might say they are of similar structure (looking at the upper 80% of the molecule). But they are different compounds. This is a most subtle form of deceit. It is, in fact, out and out dishonest, but it looks good up there on the screen at a lecture.

Let me mention in passing, that there are three stereoisomers possible for d-LSD. There are d-iso-LSD, l-LSD, and l-iso-LSD. The inversion of the stereochemistry of the attached diethylcarboxyamido group of d-LSD gives the diastereoisomer (d-iso-LSD) which is a frequent synthetic impurity of d-LSD itself. The corresponding optical antipodes l-LSD and l-iso-LSD are also known and have been tasted. All three are completely inactive: d-iso-LSD shows no psychological changes at an oral dose of 4 milligrams; l-LSD none at up to 10 milligrams orally; and l-iso-LSD none at 500 micrograms orally. These dramatic decreases in potency show both the stereoselectivity of the native LSD molecule in producing its central effects, and the LSD-free purity of these isomers.

The second major location of variations in the structure of LSD has been in the nature of the alkyl groups on the amide nitrogen atom. Some of these are Sandoz syntheses, some are from other research groups, and a few of them are found in nature. Some of these have been studied in man, and some have not. A few of the original clutch of Sandoz compounds have both 1-substituents and amide alkyl (R) group variations:

indole	— amide nitrogen substituents —		
R=	R=	R=	code name
-H	-H	-H	LA-111
-H	$-CH_3$	-H	
-H	$-CH_2CH_3$	-H	LAE-32
-H	$-(CH_2)_2CH_3$	-H	
-H	$-CH(CH_3)CH_2OH$	-H *	Ergonovine
-H	$-(CH_2)_3CH_3$	-H	
-H	$-CH(CH_3)CH_2CH_3$	-H *	
-H	$-CH(CH_2CH_3)CH_2OH$	-H *	Methergine
-H	$-(CH_2)_4CH_3$	-H	
-H	$-CH(CH_3)CH_2CH_2CH_3$	-H *	
-H	$-CH(CH_2CH_3)_2$	-H	
-H	$-(CH_2)_5CH_3$	-H	
-H	$-CH(CH_3)CH_2CH_2CH_2CH_3$	-H *	
-H	$-(CH_2)_6CH_3$	-H	
-H	$-CH(CH_3)CH_2CH_2CH_2CH_2CH_3$	-H *	
-H	$-CH_3$	$-CH_3$	DAM-57
-H	$-CH_2CH_3$	$-CH_3$	
-H	$-(CH_2)_2CH_3$	$-CH_3$	LAMP
-H	$-CH(CH_3)_2$	$-CH_3$	
-H	$-CH(CH_3)CH_2C_6H_5$	$-CH_3$ *	
-H	$-CH_2CH_3$	$-CH_2CH_3$	LSD-25
-H	$-(CH_2)_2CH_3$	$-CH_2CH_3$	
-H	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	
-H	$-CH(CH_3)_2$	$-CH(CH_3)_2$	
-H	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	DAL
-H	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	
-H	$-CH_2CH_2CH_2CH_2-$		LPD-824
-H	$-CH_2CH=CHCH_2-$		
-H	$-CH_2CH_2CH_2CH_2CH_2-$		
-H	$-CH_2CH_2OCH_2CH_2-$		LSM-775
$-CH_3$	$-CH_2CH_3$	-H	MLA-74
$-CH_3$	$-CH(CH_2CH_3)CH_2OH$	-H *	UML-491
$-COCH_3$	$-CH_2CH_3$	-H	ALA-10
$-CH_3$	$-CH_2CH_2CH_2CH_2-$		MPD-75

In the amides marked with "*" there has been the introduction of a new asymmetric center, which of course doubles the number of isomers that is possible. In each case the resulting two optical forms were prepared separately, and evaluated separately as to their pharmacology.

This listing is not intended to be thorough, but it is shown to suggest the amount of synthetic effort that has been made towards exploring and understanding the high potency associated with those two remarkably important ethyl groups on the amide nitrogen of LSD. I have given the Sandoz code names, again, as far as I know them. Although none of these really warrant a dedicated recipe, there is sufficient animal and human pharmacology reported to justify listing them below as separate items. Most of these reports appeared in the mid-1950's, but some studies are still being done, and papers are published even today with new ideas but, sadly, only with animal pharmacology. I have been as guilty as the next person who has tried to mount all these compounds into a table with a "human potency" factor that compares them directly to LSD. This is an uncomfortable simplification. Here are the actual reported observations, and I'll let the reader provide his own potency index.

LA-111, ergine, d-lysergamide. This is an active compound and has been established as a major component in morning glory seeds. It was assayed for human activity, by Albert Hofmann in self-trials back in 1947, well before this was known to be a natural compound. An i.m. administration of a 500 microgram dose led to a tired, dreamy state with an inability to maintain clear thoughts. After a short period of sleep, the effects were gone and normal baseline was recovered within five hours. Other observers have confirmed this clouding of consciousness leading to sleep. The epimer, inverted at C-8, is isoergine or d-isolysergamide, and is also a component of morning glory seeds. Hofmann tried a 2 milligram dose of this amide, and as with ergine he experienced nothing but tiredness, apathy, and a feeling of emptiness. Both compounds are probably correctly dismissed as not being a contributor to the action of these seeds. It is important to note that ergine, as well as lysergic acid itself, is listed as a Schedule III drug in the Controlled Substances Act, as a depressant. This could be, in all probability, a stratagem to control them as logical precursors to LSD.

LAE-32, N-ethyllysergamide. Different people have observed and reported different effects, with different routes of administration. Subcutaneous administrations of from 500 to 750 micrograms have been said to produce a state of apathy and sedation. Clinical studies with dosages of 500 micrograms i.m. were felt to be less effective than the control use of 100 micrograms of LSD. And yet, oral doses of twice this amount, 1.6 milligrams, have been said to produce a short-lived LSD-like effect with none of these negatives.

LPD-824, N-Pyrrolidyllysergamide. Five trials at a dosage of 800

micrograms orally led to the reporting of a fleeting effect that was similar to one tenth this amount of LSD.

LSM-775, N-Morpholinyllysergamide. There are conflicting reports; one states that 75 micrograms is an effective dose, comparable to a similar dose of LSD, and the other stated that between 350 and 700 micrograms was needed to elicit this response, and that there were fewer signs of cardiovascular stimulation and peripheral toxicity.

DAM-57, N,N-Dimethyllysergamide. This compound did induce autonomic disturbances at oral levels of some ten times the dosage required for LSD, presumably in the high hundreds of micrograms. There is some disagreement as to whether there were psychic changes observed.

DAL, N,N-Diallyllysergamide. As the tartrate salt, there is at best a touch of sparkle seen at 600 micrograms orally, but there is a sedation also reported. It is certainly an order of magnitude less potent than LSD itself.

UML-491, Methysergide, Sansert. This is the synthetic homologue of methergine (1-methyl) and is employed clinically as a treatment for migraine headaches. When the usual therapeutic dosage of two milligrams is scaled up by a factor of ten, there is a profound LSD-like response described by most subjects. A number of these ergot analogues from nature can be considered as potential precursors for the preparation of LSD. But here, there is a 1-methyl group that is effectively permanently attached, so it cannot play this role.

The third location of structural modification of the LSD molecule has been at the 6-position in ring D. This is the LAD series, with any of several alkyl groups attached to the nitrogen atom. The methyl group is found with LSD itself, and is the reason for using METH-LAD in the title as a synonym. The ethyl, allyl and propyl substitutions provide ETH-LAD, AL-LAD, and PRO-LAD, and each of these commands a separate entry.

The most frequently encountered precursor for the manufacture of LSD is ergotamine, a major alkaloid of the ergot world. It is totally unknown in the morning glories. The usual commercial form is the tartrate salt, and is often referred to under the code abbreviation of ET, for ergotamine tartrate. It has found medical use in the treatment of migraine headaches, and as an oxytocic (an agent that is used in childbirth to stimulate uterine contractions). Care with the ET terminology must be taken, in that in the drug world it has two additional associations; α-ET for alpha-ethyltryptamine and NET for N-monoethyltryptamine.

Ergonovine is a naturally occurring, water-soluble ergot alkaloid, found in both ergot preparations and in many species of morning glory seeds, and there are

several reports of LSD-like action at oral levels of between two and ten milligrams. It has an important use in obstetrics, again as an oxytocic, at about a tenth of this dose. This pharmacological potential must be respected in psychopharmacological trials. The one-carbon homologue (the butanolamide rather than the propanolamide) is called methergine or methylergonovine. It is a synthetic ally and is orally effective as an oxytocic at a dosage of 200 micrograms. It also has an LSD-like action at ten times this level.

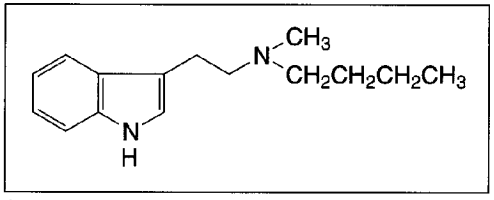
Although there are many other chemical treasures in the ergot fungal world, I would like to wrap this commentary up with a return to the topic of morning glory seeds. Four additional alkaloids of the ergot world must be acknowledged as being potentially participating factors in the MGS story. With each of these, the primary ergoline ring system is largely intact but the amide function is completely gone. The carboxyl group has been reduced to the alcohol to give elymoclavine. There is the related molecule present which is the isomer with the double bond moved to be conjugated with the aromatic ring; it is called lysergol. There is the same molecule but with a hydroxy group attached to the 8-position carbon atom (an ethyleneglycol!); it is called penniclavine. And lastly, that D-ring can actually be opened between the 5 and 6 positions, to give us a secondary amine tryptamine derivative, chanoclavine. To be completely anally retentive in this Ipomoea inventory, mention must be made of five alkaloids that are present in truly trace amounts, all of which have no oxygen atoms present whatsoever on that substitution on the ergoline 8-position. These are the 8-methyl isomers agroclavine, setoclavine, festuclavine and cycloclavine, and the methylene analogue lysergene. These structures in effect define absolute obscurity, and most probably do not contribute to the morning glory intoxication state. But the others, some present in sizable amounts, may someday help explain why the pharmacology of these seeds is so different than that of the major isolates, the ergines.

#27. MBT; TRYPTAMINE, N-BUTYL-N-METHYL; INDOLE, 3-[2-(BUTYLMETHYLAMINO)ETHYL]; N-BUTYL-N-METHYLTRYPTAMINE; 3-[2-(BUTYLMETHYLAMINO)ETHYL]-INDOLE

SYNTHESIS: To a well-stirred, ice cold solution of 5.0 g indole in 75 mL TBME, there was added a solution of 6.35 g oxalyl chloride in 25 mL CH_2Cl_2, dropwise, over the course of 15 min. Stirring was continued for an additional 10 min, and the resulting solids were removed by filtration and washed with 15 mL cold TBME. This solid amide was, in turn, added portionwise over a period of 10 min to a well-stirred, ice cold solution of 15 mL N-butyl-N-methyl amine in 100 mL CH_2Cl_2. The clear, red solution that resulted was stirred for a few additional minutes, washed in sequence with H_2O, 1% aqueous hydrochloric acid, and then H_2O. Following

drying with solid anhydrous Na_2SO_4, the solvent was removed under vacuum, yielding a thick red oil. Upon dilution with 20 mL cold EtOAc an off-white solid was produced. This was recrystallized from 100 mL boiling EtOAc producing, after cooling, filtering and air-drying to constant weight, 5.82 g of N-butyl-N-methyl-indoleglyoxylamide with a mp of 128-130 °C. A second crop of 0.6 g was obtained from the filtrate, for a total yield of 58%.

A stirred suspension of 6.3 g of N-butyl-N-methyl-indoleglyoxylamide in 150 mL dry toluene, in a three-neck, round-bottomed flask and under a N_2 atmosphere, was cooled with an external ice bath. A total of 30 mL of a 65% RED-AL solution in toluene was added slowly by syringe, and there was immediate gas evolution. After the addition was complete, the stirring was continued for an hour,



then the flask was gradually warmed to 40 °C, and the stirring continued for an additional 2 h. After cooling again to ice temperature, the excess RED-AL was decomposed by the dropwise addition of first IPA followed by (after conspicuous gas evolution had ceased) H_2O. The inorganic aluminum salts were removed by filtration of the resulting suspension, and the filter cake was washed with isopropyl acetate. The filtrate and washings were combined and washed thoroughly with H_2O. The product was then extracted into 1 N hydrochloric acid, the pooled extracts washed twice with CH_2Cl_2, made basic with 20% aqueous KOH and extracted with CH_2Cl_2. After washing with H_2O and drying with anhydrous Na_2SO_4, the solvent was removed under vacuum to yield a light yellow oil with a bluish florescence. The free amine did not crystallize but was dissolved in MeOH and titrated to a slightly basic end-point with a methanolic solution of fumaric acid. The solution was heated to the boiling point, and slowly diluted with two volumes of hot isopropyl acetate. Slow cooling yielded beautiful light yellow crystals of N-butyl-N-methyltryptamine fumarate (MBT). A recrystallization from MeOH/isopropyl acetate gave 5.83 g (69%) of product with a mp 148-150 °C.

DOSAGE: 250 - 400 mg

DURATION: 4 - 6 h

QUALITATIVE COMMENTS: (with 130 mg, orally) "Perhaps a subtle intoxication at two hours, and certainly nothing at five hours."

(with 175 mg, orally) "Some mild incoordination and concentration difficulties, all trivial, and a good sleep and a good day the next day."

(with 250 mg, orally) "At 75 minutes there was the prompt development

of an intoxicated state primarily characterized by fine motor impairment. Nothing remotely resembling any type of hallucination. Appetite was normal and food and water were consumed without difficulty. Most activities were uninteresting, even dull. The effects lasted about five hours."

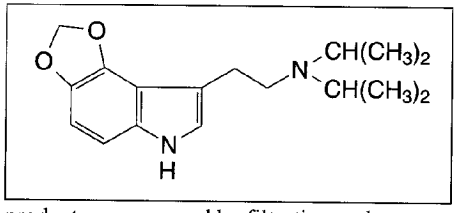
(with 400 mg, orally) "It hit in just over an hour, and it quickly became difficult to keep both eyes focused on the point of gaze. There was no actual double vision, but things were not quite right. In a few more minutes an apparent motion became apparent with fixed objects, and shortly thereafter there was a faint 'retinal circus' that was reminiscent of DMT but less compelling. Subject matter could not be chosen, but rather came on its own. At this point, walking required great concentration, and lying on a bed was a much better choice. Music seemed to encourage the drifting of thoughts, but all the eyes-closed effects faded quite quickly. I felt overheated, sweat a lot, was intensely dehydrated, and drank quantities of water all night, and still felt dehydrated. Urine output was low. Not my choice of drug; the intoxication is too much for the visual stuff."

EXTENSIONS AND COMMENTARY: This is a pretty heavy body trip for a modest mental return. As with any tertiary amine, one cannot help but speculate what role the deamination enzyme systems of the liver have in compromising the results that are being experienced. Here is a compound with five aliphatic carbon atoms hanging out there on the basic nitrogen. No branched chain; everything straight chain. How can this be compared with other tryptamines with a straight-chain on that nitrogen atom? DMT has two such carbon atoms. DET has four, DPT has six and DBT has eight. With a tally of five, MBT should lie in-between DET and DPT. Both of these show oral activity in the 300 milligram range (as does MBT) but at least DET has some five-fold increased potency if given parenterally. I really would like to see this particular compound explored by smoking, or injection, or even orally with some effective monoamine oxidase inhibitor on board (a dose of *P. harmala,* maybe) and see if there can be more mental effects and fewer toxic effects at a lower dose exposure. There is certainly good precedent for it, amongst the other dialkyl tryptamines.

A structural isomer has been made, with the butyl group branched at the nitrogen atom. This is N-s-butyl-N-methyltryptamine, or MSBT. It came from a two-pass alkylation of N-methyltryptamine (NMT) with s-butyl bromide in isopropylalcohol in the presence of solid potassium iodide. It remained an oil, but was over 90% pure by GCMS, with unreacted NMT being the major impurity. MS (in m/z): $C_6H_{14}N$+ 100 (100%); indolemethylene+ 130 (8%); parent ion 230 (1%). It has been assayed in man, but it remains an unknown.

#28. 4,5-MDO-DIPT; TRYPTAMINE, N,N-DIISOPROPYL-4,5-METHYLENEDIOXY; INDOLE, 3-[2-(DIISOPROPYLAMINO)ETHYL]-4,5-METHYLENEDIOXY; N,N-DIISOPROPYL-4,5-METHYLENEDIOXYTRYPTAMINE; 3-[2-(DIISOPROPYLAMINO)ETHYL]-4,5-METHYLENEDIOXYINDOLE; 5H-1,3-DIOXOLO-[4,5-E]INDOLE-7-ETHANEAMINE, N,N-DIISOPROPYL

SYNTHESIS: A solution of 4.8 g 4,5-methylenedioxyindole (see under 4,5-MDO-DMT for its preparation) in 60 mL anhydrous Et_2O was stirred and cooled with an external ice bath. There was added, dropwise, a solution of 5.0 g oxalyl chloride in Et_2O so that the temperature did not exceed 5 °C. The intermediate acid chloride separated as a red solid, and was removed by filtration and washed with Et_2O. It was



then suspended in 60 mL cold anhydrous Et_2O, treated with 14 mL diisopropylamine and the mixture stirred for 30 min. The solvent was decanted from the crude solids that formed, and they were suspended in 50 mL H_2O. The product was removed by filtration and vacuum-dried to provide 5.3 g (56%) N,N-diisopropyl-4,5-methylenedioxyindole-3-glyoxylamide as white solid, with a mp 260 °C (dec).

To a stirred and cooled solution of 3.8 g LAH in 100 mL anhydrous THF there was added, over the course of 1 h, a solution of 4.70 g N,N-diisopropyl-4,5-methylenedioxyindole-3-glyoxylamide in 500 mL anhydrous THF. After 1 h reflux, the cooled reaction mixture was treated with 3.8 mL H_2O, followed by 3.8 mL aqueous 5% NaOH and then by an additional 10.4 mL H_2O. The solids were removed by filtration and washed with THF. The combined filtrate and washings were dried ($MgSO_4$) and the solvent removed under vacuum. The residual oil was distilled at the KugelRohr (0.5 mm/Hg at 100 °C) to give a distillate that solidified. This was crystallized from benzene/hexane to provide 1.34 g (31%) of N,N-diisopropyl-4,5-methylenedioxytryptamine (4,5-MDO-DIPT) with a mp of 109-113 °C. Anal: C, H. N.

DOSAGE: > 25 mg, orally

DURATION: unknown

QUALITATIVE COMMENTS: (25 mg, orally) "Nothing much happened for about 3 hours, and then I suddenly shot up. I was at the plateau for a fair time, the recovery was difficult to define chronologically. This was in daylight; I was reminded very much of LSD."

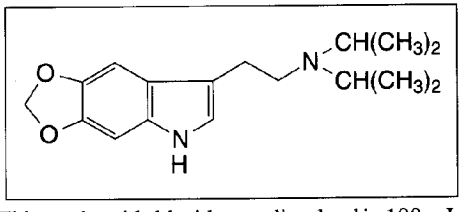
EXTENSIONS AND COMMENTARY: This is one of the two tryptamines reported here with the most appealing methylenedioxy ring bridge located at the two most sensitive ring positions of the indole nucleus. It, too, is an unknown entity. There is a single observation of an oral trial, and it suggests something of interest at 25 milligrams. Higher dosages might prove most interesting. There is no question that the methyl isopropyl homologue of this compound, 4,5-MDO-MIPT, would be a rewarding compound to assay. As of the present moment, it has not yet been synthesized. It should be a relatively easy one to make.

There is an interesting parallel to be seen here. This methylenedioxy hetero-ring is snuggled as closely as possible to the ethylamine chain of the indole (the 4-position occupied by the nearer oxygen atom, and the indole chain at the 3-position). The same intimacy is possible in the phenethylamine world. This would be realized by moving the methylenedioxy ring of MDA (3,4-methylenedioxyamphetamine) to the 2,3-location. Here, again, the nearer oxygen would be as close as possible to the ethylamine chain at the 1-position. This compound, 2,3-methylenedioxyamphetamine, has been made by several research groups, and has been looked at in man. At 50 milligrams, orally, it produced some pretty strong stimulatory effects, with no sleep found to be possible during the following 24 hours. But, on the other hand, it seemed to be devoid of MDA-like effects. This positional isomer was mentioned in PIHKAL.

There is no way to meaningfully extrapolate from this phenethylamine analogue, 2,3-MDA, to 4,5-MDO-DIPT, but it does present a very close structural relationship that could be used to justify a clinical study of this unusual tryptamine.

#29. 5,6-MDO-DIPT; TRYPTAMINE, N,N-DIISOPROPYL-5,6-METHYLENEDIOXY; INDOLE, 3-[2-(DIISOPROPYLAMINO)ETHYL]-5,6-METHYLENEDIOXY; N,N-DIISOPROPYL-5,6-METHYLENEDIOXY-TRYPTAMINE; 3-[2-(DIISOPROPYLAMINO)ETHYL]-5,6-METHYL-ENEDIOXYINDOLE; 5H-1,3-DIOXOLO-[4,5-F]INDOLE-7-ETHANE-AMINE, N,N-DIISOPROPYL

SYNTHESIS: To a well-stirred, cold solution of 1.61 g 5,6-methylenedioxyindole (see under 5,6-MDO-MIPT for its preparation) in 20 mL anhydrous Et_2O, there was added dropwise a solution of 1.75 mL oxalyl chloride in 5 mL Et_2O. The addition took 20 min. After an additional 20 min stirring in the external ice bath, the red crystals that formed were removed by filtration, washed with 2x5 mL Et_2O, and dried under vacuum for 0.5 h. This crude acid chloride was dissolved in 100 mL



anhydrous THF and cooled, under N_2, to 0° C. An Et_2O solution of diisopropylamine was added until the reaction mixture remained basic (pH >9 to external pH paper). The solvents were removed under vacuum, and residue treated with 100 mL each of H_2O and $CHCl_3$. The organic phase was separated, the aqueous phase extracted with additional $CHCl_3$, the pooled extracts dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated under vacuum. The residue was recrystallized from ethyl acetate/hexane to yield 1.20 g N,N-diisopropyl-5,6-methylenedioxyindol-3-ylglyoxylamide with a mp 278-280 °C (38%). Anal: C,H,N.

To a well-stirred suspension of 0.77 g of LAH in 40 mL dry THF, there was added, dropwise, a solution of 0.95 g N,N-diisopropyl-5,6-methylenedioxyindol-3-ylglyoxylamide in approximately 100 mL of anhydrous THF. The mixture was brought to reflux temperature and held there for 2 h, and allowed to return to room temperature. It was hydrolyzed by the cautious addition of 0.8 mL H_2O, followed with 2.4 mL 10% aqueous NaOH, and finally an additional 0.8 mL of H_2O. The inorganics were removed by filtration through Celite, and the filtercake was washed with additional THF. After removal of the solvent of the combined filtrate and washings under vacuum, the residue was distilled by KugelRohr and the colorless distillate recrystallized from a mixture of Et_2O/hexane. There was thus obtained 0.52 g N,N-diisopropyl-5,6-methylenedioxytryptamine (5,6-MDO-DIPT) with a melting point of 93-94 °C (60%). Anal: C,H,N.

DOSAGE: Unknown

DURATION: Unknown

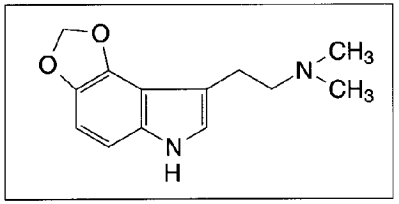
EXTENSIONS AND COMMENTARY: So why enter an entry into a listing of active compounds when it is simply not known if it is active or not? The truth is that none of these three 5,6-methylenedioxy-N,N-disubstituted tryptamines (this one, or 5,6-MDO-DMT or 5,6-MDO-MIPT) have been explored up to an active level, but they are appealing targets in that they have the progression of nitrogen substituents that has proven so valuable in similar sequences of compounds. This is the pattern dimethyl, methylisopropyl and diisopropyl. With both the unsubstituted, and the 5-methoxy-substituted groups, the activity goes from quite potent but requiring parenteral administration, to highly potent and orally active, and back to quite potent and orally active, as the methyl groups are progressively replaced with isopropyl groups. It would be instructive to see if this arrangement was maintained with this methylenedioxy trilogy.

The three kinds of closed-ring substituents mentioned in the pyr-T recipe have also been described with this 5,6-methylenedioxy ring substitution. These could be named 5,6-MDO-pyr-T (the pyrrolidine analogue, mp 110-112 °C), 5,6-MDO-pip-T (the piperidine analogue, mp 150-152 °C) and 5,6-MDO-mor-T (the morpholine analogue, mp 117-119 °C). To my knowledge, none of these have ever been put into man.

#30. 4,5-MDO-DMT; TRYPTAMINE, N,N-DIMETHYL-4,5-METHYLENEDIOXY; INDOLE, 3-[2-(DIMETHYLAMINO)ETHYL]-4,5-METHYLENEDIOXY; N,N-DIMETHYL-4,5-METHYLENEDIOXYTRYPTAMINE; 3-[2-(DIMETHYLAMINO)ETHYL]-4,5-METHYLENEDIOXYINDOLE; 5H-1,3-DIOXOLO-[4,5-E]INDOLE-7-ETHANEAMINE, N,N-DIMETHYL

SYNTHESIS: To a well-stirred H_2O suspension (160 mL) of 3.7 g methyltrialkylammonium chloride (Adogen 464) and 138 mL CH_2Br_2 (under nitrogen), there was added a solution of 100 g 3-methylcatechol in 400 mL H_2O containing 80 g NaOH, over the course of 2 h. Stirring was continued for 1 h, then the reaction mixture was subjected to steam distillation. The distillate was cooled, and the phases separated. Extraction of the aqueous phase with CH_2Cl_2, pooling of the organic phases, and removal of the solvent under vacuum, yielded 85 g (78%) of 2,3-methylenedioxytoluene as a colorless oil.

A mixture of 21 g 2,3-methylenedioxytoluene and 1 g $Hg(OAc)_2$ in 60 mL acetic acid was stirred and heated to 80 °C. To this there was added, dropwise, 12.8 g of concentrated nitric acid. Heating and stirring was continued for 2 h. The reaction mixture was quenched by pouring it into ice-H_2O, and extracted with Et_2O. The extracts were pooled, dried with anhydrous $MgSO_4$, and the volatiles removed under vacuum. The orange solid residue was recrystallized from EtOH to provide 20 g (58%) of a mixture of the ortho- and meta-products, 2,3-methylenedioxy-5-nitrotoluene and 2,3-methylenedioxy-6-nitrotoluene, with a mp 65-67 °C. This unresolved mixture was employed in the next step without further purification.



In a flask equipped with a total reflux packed column and a variable take-off head, 15.0 g of the 2,3-methylenedioxy-5-nitrotoluene/2,3-methylenedioxy-6-nitrotoluene mix was added to a mixture of 100 mL freshly distilled DMF and 12.8 g of N,N-dimethylformamide dimethyl acetal. The reaction mixture was heated to a controlled reflux that kept the head temperature at 50 to 70 °C, allowing the removal of MeOH. After 4 h, 90% of the theoretical amount of MeOH (7.4 mL) had been distilled off, and the residual solvent (DMF) was removed under vacuum. The dark residue was dissolved in benzene, washed with H_2O, dried with anhydrous $MgSO_4$, and the solvent removed under vacuum. The crude crystalline product was recrystallized from hexane/benzene to provide 4.8 g (50%) of 2,3-methylenedioxy-6-nitro-beta-dimethylaminostyrene as red needles with a mp 126-128 °C.

A solution of 3.5 g 2,3-methylenedioxy-6-nitro-beta-dimethylaminostryrene in 200 mL benzene was placed in a Parr hydrogenation bomb and treated with 0.35 g of 10% Pd/C. The mixture was shaken for 7 h under 3 atm H_2.

The catalyst was removed by filtration, and the filtrate was washed first with 2N H_2SO_4, followed by aqueous $NaHCO_3$ and H_2O. This was dried and the solvent removed under vacuum to give 1.2 g (50%) of 4,5-methylenedioxyindole as a residue. After crystallization from benzene/petroleum ether, it had a mp 111 °C. Anal: C,H,N.

A solution of 4.8 g 4,5-methylenedioxyindole in 60 mL anhydrous Et_2O was stirred and cooled with an external ice bath. There was added, dropwise, a solution of 5.0 g oxalyl chloride in Et_2O so that the temperature did not exceed 5 °C. The intermediate acid chloride separated as a red solid, and was removed by filtration and washed with Et_2O. It was then suspended in 60 mL cold anhydrous Et_2O, treated with 7 mL dimethylamine and the mixture stirred for 30 min. The solvent was decanted from the crude solids that formed, and they were suspended in 50 mL H_2O. The product was removed by filtration and vacuum dried to provide 5.7 g (77%) N,N-dimethyl-4,5-methylenedioxyindole-3-glyoxylamide as a white solid with a mp 240-243 °C.

To a stirred and cooled solution of 3.8 g LAH in 100 mL anhydrous THF there was added, over the course of 1 h, a solution of 3.7 g N,N-dimethyl-4,5-methylenedioxyindole-3-glyoxylamide in 500 mL anhydrous THF. After 1 h reflux, the cooled reaction mixture was treated with 3.8 mL H_2O, followed by 3.8 mL 5% NaOH and then by an additional 10.4 mL H_2O. The solids were removed by filtration and washed with THF. The combined filtrate and washings were dried ($MgSO_4$) and the solvent removed under vacuum. The residual oil was distilled at the KugelRohr (0.5 mm/Hg at 100 °C) to give a distillate that solidified. This was crystallized from benzene/petroleum ether to provide 0.25 g (8%) of N,N-dimethyl-4,5-methylenedioxytryptamine (4,5-MDO-DMT) with a mp of 93-95 °C. Anal: C, H. N.

DOSAGE: unknown

DURATION: unknown

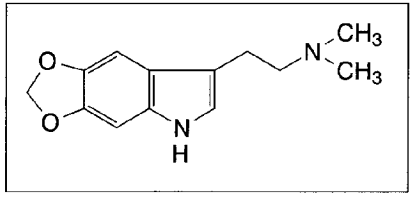
EXTENSIONS AND COMMENTARY: The two aromatic ring positions that are associated with human psychedelic activity are the 4-position (of psilocybin fame) and the 5-position (of 5-methoxy-this-and-that fame). Here is a compound with both positions oxygen-substituted (with the methylenedioxy ring that is so effective in the phenethylamine world) and it has not been looked at in man, to my knowledge. I snooped around in the literature associated with this kind of DMT substitution, and the world of di-oxygen substitution to be found at these two potent focal points is almost unknown. Aside from the 4,5-methylenedioxy-diisopropyltryptamine, described here in the recipes (under 4,5-MDO-DIPT), there are only five of these dioxygenated compounds known. 4-benzyloxy-5-methoxy-tryptamine is the precursor of the DMT and DET homologues with a 4-hydroxy group exposed after hydrogenation. But nowhere is there a 4,5-dimethoxy pattern.

In fact the methoxy group is unknown in the 4-position in this simple system.

I have been told that Mark Julia, in France, had made the 4-hydroxy-5-methoxy compound with a methyl and an ethyl on the tryptamine nitrogen. If so, it certainly is not in the literature abstracts and thus is of unknown properties. I want to search this out.

#31. 5,6-MDO-DMT; TRYPTAMINE, N,N-DIMETHYL-5,6-METHYLENEDIOXY; INDOLE,3-[2-(DIMETHYLAMINO)ETHYL]-5,6-METHYLENEDIOXY; N,N-DIMETHYL-5,6-METHYLENEDIOXY-TRYPTAMINE; 3-[2-(DIMETHYLAMINO)ETHYL]-5,6-METHYLENE-DIOXYINDOLE; 5H-1,3-DIOXOLO-[4,5-F]INDOLE-7-ETHANEAMINE, N,N-DIMETHYL

SYNTHESIS: To a well-stirred, cold solution of 1.61 g 5,6-methylenedioxyindole (see under 5,6-MDO-MIPT for its preparation) in 20 mL anhydrous Et_2O, there was added, dropwise, a solution of 1.75 mL oxalyl chloride in 5 mL Et_2O. The addition took 20 min. After an additional 20 min stirring in the external ice bath, the red crystals that formed were removed by filtration, washed with 2x5 mL Et_2O, and dried under vacuum for 0.5 h. This crude acid chloride was dissolved in 100 mL anhydrous THF and cooled, under N_2, to 0° C. An Et_2O solution of dimethylamine was added until the reaction mixture remained basic (pH >9 to external pH paper). The solvents were removed under vacuum, and the residue treated with 100 mL each of H_2O and $CHCl_3$. The organic phase was separated, the aqueous phase extracted with additional $CHCl_3$, the pooled extracts dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated under vacuum. The residue was recrystallized from ethanol/EtOAc to yield 1.07 g N,N-dimethyl-5,6-methylenedioxy-4-indoleglyoxylamide with a mp of 225-226 °C (yield 41%). Anal: C,H,N.



To a well-stirred suspension of 0.77 g of LAH in 40 mL dry THF, there was added, dropwise, a solution of 0.87 g N,N-dimethyl-5,6-methylenedioxy-4-indoleglyoxylamide in approximately 100 mL of anhydrous THF. The mixture was brought to reflux temperature, held there for 2 h, and allowed to return to room temperature. It was hydrolyzed by the cautious addition of 0.8 mL H_2O, followed with 2.4 mL 10% aqueous NaOH, and an additional 0.8 mL of H_2O. The inorganics were removed by filtration through Celite, and the filtercake was washed with additional THF. After removal of the solvent of the combined filtrate and washings under vacuum, the residue was distilled at the KugelRohr and the colorless distillate recrystallized from a mixture of EtOAc/hexane. There was obtained 0.30 g (38%) N,N-dimethyl-5,6-methylenedioxytryptamine (5,6-MDO-DMT), mp 115-117 °C.

DOSAGE: Greater than 5 mg

DURATION: Unknown

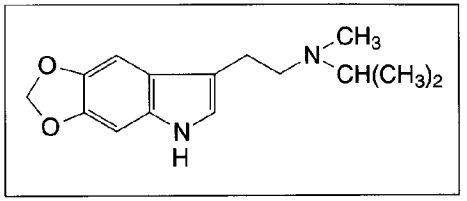
QUALITATIVE COMMENTS: (with 5 mg, smoked) "Nothing."

EXTENSIONS AND COMMENTARY: Up until 15 years ago, there had been no research published describing any simple N,N-disubstituted tryptamines carrying the methylenedioxy substitution pattern on the indole ring. This is interesting in that the activity of the methylenedioxy substituted phenethylamine MDA had been well documented almost 40 years ago, and its N-methyl homologue MDMA has been of known human activity for about 25 years. Then, within a year, two papers appeared in the literature describing both this compound (5,6-MDO-DMT) and the corresponding N,N-diisopropyl homologue, 5,6-MDO-DIPT. As to the position of this five-membered ring, there are two appealing locations. The 5,6-pattern has an appealing symmetry to it, being closely parallel to MDA, with a sortof long axis extending through the tryptamine molecule from the 3-position (where the side chain is attached), across the indole ring, coming out between the 5- and 6- positions. This certainly feels like the most natural analogue to MDA or MDMA. It has the plus of having the important 5-position occupied, but there might be a bit of a negative effect due to its having something at the 6-position. A more exciting possibility would be the 4,5-disubstitution, which would involve the favorite 5-position along with the site of the oxygen atom of psilocin and psilocybin. This compound has been made and is the preceding recipe, 4,5-MDO-DMT, #30.

As to the nature of the nitrogen substituents, this N,N-dimethyl compound is directly analogous to its 5-methoxy or 5-hydrogen counterparts. In behavioral studies, it is less potent than either of these simpler compounds, 5-MeO-DMT or DMT. In human studies these latter two chemicals are both active at levels of a few milligrams, and a trial with 5,6-MDO-DMT showed no activity at all at a five milligram trial. More studies are needed, and I am sure that, in time, they will be carried out.

#32. 5,6-MDO-MIPT; TRYPTAMINE, N-ISOPROPYL-N-METHYL-5,6-METHYLENEDIOXY; INDOLE, 3-[2-(ISOPROPYLMETHYLAMINO)-ETHYL]-5,6-METHYLENEDIOXY; N-ISOPROPYL-N-METHYL-5,6-METHYLENEDIOXYTRYPTAMINE; 3-[2-(ISOPROPYLMETHYL-AMINO)ETHYL]-5,6-METHYLENEDIOXYINDOLE; 5H-1,3-DIOXOLO-[4,5-F]INDOLE-7-ETHANEAMINE, N-ISOPROPYL-N-METHYL

SYNTHESIS: To 500 mL concentrated nitric acid, stirred and cooled with an external ice-bath there was added, a bit at a time, 50 g of finely powdered piperonal. The temperature must not be allowed to rise above 0 °C during the addition. After two hours of additional stirring, the reaction was poured over chipped ice, the product removed by filtration and washed with H_2O to remove all traces of acid. After recrystallization from a 50/50 mixture of EtOAc and EtOH, the product, 2-nitro-4,5-methylenedioxybenzaldehyde, was obtained as lemon-yellow colored crystals that weighed 47 g when dry, and had a mp of 97-98 °C.



A solution of 43.8 g 2-nitro-4,5-methylenedioxybenzaldehyde in 225 mL glacial acetic acid was treated with 66.2 g nitromethane followed by 29.2 g anhydrous ammonium acetate. After being held at reflux for 2 h, the volume was reduced to approximately half by distillation, and the residues poured into ice water. The solids were removed quickly by filtration, washed well with H_2O, and air-dried. An analytical sample of 2,2'-dinitro-4,5-methylenedioxystyrene was obtained as yellow crystals by crystallization from EtOH and had a mp of 121-122 °C. The unpurified isolate can be used directly in the next step.

A round-bottom flask was equipped with a mechanical stirrer, a reflux condenser, and a means of cooling with an external water bath. To 165 mL glacial acetic acid there was added 21 g 2,2'-dinitro-4,5-methylenedioxystyrene and 82 g powdered elemental iron. With good stirring, gentle heating was applied until an exothermic reaction set in, and this was maintained at a controlled pace with external cooling. When the spontaneous reaction had subsided, the reaction was brought to reflux for 15 min, then quenched by addition to a solution of 120 g NaOH in 500 mL H_2O. The reaction mixture was subjected to steam distillation and the distillate (25 L) was extracted several times with Et_2O. These extracts were combined, the solvent removed under vacuum, and the residue crystallized from petroleum ether. There was thus obtained 4.7 g of 5,6-methylenedioxyindole as colorless plates with a melting point of 108-110 °C, for a yield of 33% of theory. Catalytic hydrogenation is an alternate process for reduction. To a solution of 19.12 g 2,2'-dinitro-4,5-methylenedioxystyrene in a mixture of 55 mL absolute EtOH, 40 mL acetic acid and 300 mL EtOAc, there was added 4 g 10% palladium on charcoal and the reaction was shaken under 55 psi hydrogen for 45 minutes. After filtration through Celite under an inert atmosphere, the filtrate was treated with a suspension of 40 g $NaHCO_3$ in 100 mL H_2O. The organic phase was dried over anhydrous $MgSO_4$, then the solvent was removed under vacuum. The greenish-black residue was triturated with 4x100 mL portions of boiling cyclohexane. The extracts were combined and cooled, allowing the crystallization of the product 5,6-methylenedioxyindole as a solid with a mp of 107-110 °C. The yield was 8.3 g (64%).

To a well-stirred, cold solution of 1.61 g 5,6-methylenedioxyindole in 20 mL anhydrous Et_2O, there was added, dropwise, a solution of 1.75 mL oxalyl chloride in 5 mL Et_2O. The addition took 20 min. After an additional 20 min stirring, the red crystals that formed were removed by filtration, washed with 2x5 mL Et_2O, and dried under vacuum for 0.5 h. This crude acid chloride was dissolved in 100 mL anhydrous THF and cooled to 0° C with stirring under N_2. An Et_2O solution of N-isopropyl-N-methylamine was added until the reaction mixture remained basic (pH >9 to external pH paper). The solvents were removed under vacuum, and the residue treated with 100 mL each of H_2O and $CHCl_3$. The organic phase was separated, the aqueous phase extracted with additional $CHCl_3$, the pooled extracts dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated under vacuum. The residue was recrystallized from acetone to yield 1.47 g N-isopropyl-N-methyl-5,6-methylenedioxy-3-indoleglyoxylamide with a mp 203-204 °C. Anal: C,H,N.

To a well-stirred suspension of 1.15 g of LAH in 60 mL dry THF, there was added, dropwise, a solution of 1.44 g N-isopropyl-N-methyl-5,6-methylenedioxy-3-indoleglyoxylamide in approximately 150 mL of anhydrous THF. The mixture was brought to reflux temperature, held there for 2 h, and allowed to return to room temperature. It was hydrolyzed by the cautious addition of 1.15 mL H_2O, followed with 3.5 mL 10% aqueous NaOH, and finally an additional mL of H_2O. The inorganics were removed by filtration through Celite, and the filtercake was washed with additional THF. After removal of the solvent of the combined filtrate and washings under vacuum, the residue was distilled at the KugelRohr and the colorless distillate recrystallized from a mixture of benzene and cyclohexane. There was thus obtained 0.43 g N-isopropyl-N-methyl-5,6-methylenedioxytryptamine (5,6-MDO-MIPT) with a melting point of 87-89 °C (33%). Anal: C,H,N. MS (in m/z): $C_5C_{12}N^+$ 86 (100%); indolemethylene$^+$ 174 (7%); parent ion 260 (9%).

DOSAGE: > 50 mg, orally

DURATION: Unknown

QUALITATIVE COMMENTS: (with 35 mg, orally) "Some paresthesia noted. Nothing else."

(with 50 mg, orally) "Maybe a trace of activity after an hour. Certainly nothing at three hours."

(with 60 mg, orally) "There is something going on there, but I can't tell what it is. Very vague."

(with 75 mg, orally) "Just a teasing smell of light-headedness in twenty minutes, and maybe a bit more light-headedness in an hour. I can suspect the chronology, but the character of the effects remains nebulous. It is certainly less dramatic than the 5-methoxy-compound."

EXTENSIONS AND COMMENTARY: I must continuously struggle with the reality that the substitutions on the indole ring demand an analogy to those on the phenethylamine ring. Clearly the 4-substituent is important, and the 5-substituent calls the shots (as with the 4-substituent in the phenethylamines). But is it possible that anything at the six-position is the kiss of death?

Both the 4,5-dimethoxy and the 5,6-dimethoxy-analogues are well established, and they would be fantastic tools to help unravel this problem. Clearly the 5,6-methylenedioxy materials are not too interesting, whereas the 4,5-methylenedioxy-counterparts have the rich smells of interest.

A totally compelling incident occurred in the course of writing this commentary. I decided not to assume that the reader had access to commercially available 5,6-methylenedioxyindole, but just might want to make it himself. It has been prepared from piperonal, and I said to myself, why not put into the recipe a dull but useful preparation from the ancient literature? So, let's find the 1967 article in the *Monatsh. Chem.* and translate the original German instructions into English for the readers. Simple and straight-forward? Yes? No!

A bit of background. Years ago, the fantastic library at the Medical School at San Francisco got into a bit of space and storage problems, and had to put its older reference issues in some sort of storage status, and it became necessary to get volumes brought out of hiding as you needed them. OK. We don't have the space. I can buy that. Let's get the space. So, a new library was designed to bring all reference material into one location and thus allow the researcher access to anything and everything he needed. Big money was asked for and big money was gotten. Finally, a single research source was created that appeared to meet all these needs. It was a multi-story giant across the street from the old medical school buildings. A treasure for the medical center, with all things for all people. So I tried to find Volume 98 of *Monatsh. Chem.*, published in 1967, with the details of the nitration of piperonal. No problem. The call number was W1 MO 343, so I go down three floors into the W1 territory, and I discover that there is nothing in the MO 343 section. Nothing but empty shelves. I find a helpful man who confirms that the volumes are missing, and then he asks me, "Are they pre-1975?" "Well, yes, they are." "Are they in a foreign language?" "Yes, in German." "Well," he says, "They have probably been moved over across the bay to Richmond, for safe keeping." "Is it a space problem?" "No, it deals with preservation and deterioration." "You are saying that older German text journals are more fragile than English counterparts?" "Well, it's a precautionary move."

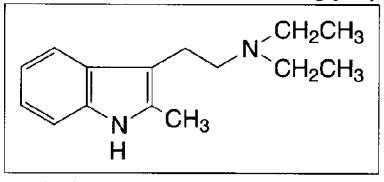
The next day, I phoned in my needs to Richmond and was assured that when I got there the volume I needed would be immediately available at noon as I had asked. I made two errors in navigation in my search for the Richmond Agricultural Field Station, and located the Earthquake Research Library first. But I was met with total courtesy and was supplied with improved directions. It turned out that the field library had a Xerox machine than needed nickels, and I happened

to have a pile of nickels. And I now have my recipe for the nitration of piperonal firmly in hand. But I also got a feeling that the priorities of those who needed to use reference libraries might be in conflict with the priorities of those who controlled these reference libraries.

I plead a most simple case to all of these authorities. I will in the future, on occasion, need a reference. Please let me have access to that reference when I need it. I see all these obstacles you might raise to my free access to any particular reference as a form of censorship, and I see it as a small but real measure of the superimposition of your principles upon mine. In a word, Mr. University, let me find what I want to find. Let me read what I want to read. Let me copy what I want to copy. In short, Mr. University, play the role that your founders intended you to play. My taxes paid for you; stay out of my way.

#33. 2-Me-DET; TRYPTAMINE, N,N-DIETHYL-2-METHYL; INDOLE, 3-[2-(DIETHYLAMINO)ETHYL]-2-METHYL; N,N-DIETHYL-2-METHYLTRYPTAMINE; 3-[2-(DIETHYLAMINO)ETHYL]-2-METHYL-INDOLE

SYNTHESIS: To an ice-cold and stirred solution of 6.56 g 2-methylindole in 75 mL TBME there was added, over the course of 20 min, 35 mL of a 2.0 M solution of oxalyl chloride in CH_2Cl_2. The glyoxyl chloride formed immediately and was removed by filtration and washed with 20 mL cold TBME. A solution of 16 mL diethylamine in 50 mL CH_2Cl_2 was prepared, cooled in an external ice bath, and vigorously stirred. To this, the solid glyoxyl chloride was added in small increments, producing a yellow solution. The reaction mixture was washed successively with H_2O, 0.5 N HCl, and again with H_2O. After drying over anhydrous Na_2SO_4, the solvent was removed under vacuum, providing an orange solid as residue. This was recrystallized from boiling THF and, after filtration and air drying to constant weight, provided N,N-diethyl-2-methylindoleglyoxylamide with a mp 170-172 °C.



To a stirred and cooled solution of 7.4 g N,N-diethyl-2-methylindole–glyoxylamide in 80 mL dry toluene under an inert atmosphere, there was added 31 mL 65% RED-AL in toluene, at a slow rate. After 20 min the ice bath was removed and the reaction allowed to stir for 2 h, and finally an additional 3 h at 60 °C. The light yellow solution was cooled again in the ice bath, and the excess hydride destroyed by the slow addition of 15 mL IPA followed by 50 mL H_2O. The solids were removed by filtration and washed with toluene. The combined filtrate and washings were repeatedly washed with H_2O and then extracted twice with 0.5 N HCl. The aqueous extracts were pooled, washed with CH_2Cl_2, and made basic by the addition of 25% NaOH. The precipitate that formed was extracted into several small portions of CH_2Cl_2 which were pooled and dried with anhydrous Na_2SO_4. After removal of the drying agent, the solvent was removed under vacuum. To the residue there was added a 1.0 M solution of HCl in anhydrous Et_2O until the mixture was neutral, as determined by external, damp pH paper. The resulting solid was removed by filtration and twice recrystallized from a MeOH/acetone mixed solvent. There was thus obtained N,N-diethyl-2-methyltryptamine hydrochloride (2-Me-DET) as white crystals with a mp 214-216 °C.

DOSAGE: 80 - 120 mg, orally

DURATION: 6 - 8 h

QUALITATIVE COMMENTS: (with 70 mg, orally) "A very subtle onset characterized most notably as a mild stomach ache that lasted a short while. There was a sort of vague unreal feeling at an hour, but my thought pattern seemed to be quite clear. In another hour I noticed that higher pitches of the music on the radio were being muffled and the tones seemed to be shifting to lower frequency. I phoned a friend, and first the dial tone, and then her voice sounded wrong. The sense of touch (the phone receiver) was normal and my conversation flowed easily. Television seemed amusing, but perhaps it really was amusing. Soup tasted fine, and there was no appetite suppression. No GI problems, no next-day negatives."

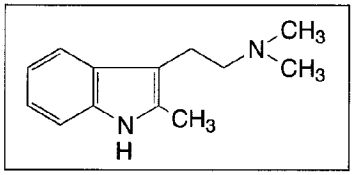
(with 120 mg, orally) "My thoughts became quite cloudy, increasingly so for several hours. And somehow slower than usual. Reading didn't seem to connect, and I had to turn the radio off as it was lousy. Texture, not content. I could type OK, and did, so my body was OK, but things came to me slowly. I wasn't very hungry but food tasted OK. The 'cloudy' was pretty much gone after six hours. I don't particularly want to repeat this, as there isn't much here that I enjoy."

EXTENSIONS AND COMMENTARY: There is an interesting idea tucked away here in what seems to be an uninteresting compound.

The sound distortion, mentioned in both of these reports, brings to mind DIPT, where it is the major indicator of intoxication. With some people, it is the only change observed. With DIPT, there are two isopropyl groups on the basic nitrogen atom; here there are two ethyl groups. One might speculate that there might well be some optimum group geometry that would make the auditory to visual distortion ratio as high as possible. There were no suggestions that there were any auditory changes with DET so perhaps the added mass of that methyl group at the 2-position brings the molecular weight into some "auditory window." A compelling compound would be, of course, N,N-diisopropyl-2-methyltryptamine (2-Me-DIPT), but I don't believe that it has ever even been synthesized as of the present moment. It would certainly be a simple compound to make from the above indole.

#34. 2-Me-DMT; 2,N,N-TMT; TRYPTAMINE, 2,N,N-TRIMETHYL; INDOLE, 3-[2-(DIMETHYLAMINO)ETHYL]-2-METHYL; 2,N,N-TRIMETHYLTRYPTAMINE; 3-[2-(DIMETHYLAMINO)ETHYL]-2-METHYLINDOLE; DESMETHOXY-INDAPEX

SYNTHESIS: To a stirred, ice-cooled solution of 1.31 g 2-methylindole in 30 mL TBME, there was added 7.5 mL of a 2M solution of oxalyl chloride in CH_2Cl_2, dropwise. An orange-red precipitate formed when the addition was half complete.



The solid product was removed by filtration, and washed with another 30 mL of cold TBME. This material was added, in small portions, to an ice-cold mixture of 3.5 mL 40% aqueous dimethylamine and 30 mL CH_2Cl_2 that was being vigorously stirred. The acid chloride faded to a pale yellow immediately on contact with the reaction medium. After the addition was completed, the organic phase was washed with H_2O, dilute HCl, and again with water. After drying over anhydrous Na_2SO_4, the solvent was removed under vacuum to yield a yellow glass as residue. Scratching with a warm isopropyl acetate cyclohexane mixture successfully induced crystallization, and there was thus obtained 0.84 g of 2,N,N-trimethylindoleglyoxylamide with mp 167-170 °C.

A stirred solution of 3.8 g 2,N,N-trimethylindoleglyoxylamide in 70 mL dry toluene was placed under a nitrogen pad and cooled with an external ice bath. There was then added 25 mL of a 60% solution of sodium bis(2-methoxyethoxy)–aluminumhydride in toluene (RED-AL). The stirring was continued at 0 °C for 30 min, then brought to room temperature for an additional 2 h. After cooling again, the excess hydride was destroyed by the dropwise addition of IPA, and (when the gas evolution had ceased) H_2O was added with caution. The aluminum salts were removed by filtration, and washed with isopropyl acetate. The filtrate and washes were combined, washed with H_2O, then extracted with dilute HCl. After washing the aqueous phase with CH_2Cl_2, it was made basic with 20% aqueous KOH, and extracted with CH_2Cl_2. The pooled extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and the solvent removed under vacuum. The residue was dissolved in a small amount of MeOH and brought to a neutral pH with the careful addition of fumaric acid in MeOH. Removal of the solvent under vacuum gave a white crystalline residue which was washed with isopropyl acetate, and recrystallized from a MeOH/isopropyl acetate mixture. There was thus obtained 1.8 g 2-methyl-N,N-dimethyltryptamine fumarate (2-Me-DMT) as colorless crystals with mp 205-208 °C.

The compound has also been synthesized from 2-methylindole-3-acetic acid via the ethyl ester, to the ethanol with sodium and alcohol, to the ethyl bromide with PBr_3 in Et_2O, to the product (2-Me-DMT) with dimethylamine. The reported mp

of the free base is 97-98 °C.

DOSAGE: 50 - 100 mg, orally

DURATION: 4 - 6 h

QUALITATIVE COMMENTS: (with 50 mg, orally) "There was tingling everywhere but it faded after about three hours. Nothing else."

(with 75 mg, orally) "Very mild stomach rumbling during the first hour, with no other effects until the 65 minute point. Then there was the onset of a very mild relaxed feeling followed by intermittent skin alerting, especially on the head and neck. No visuals. Sexual activity at 90 minutes showed marked enhancement of both the pre-climactic and orgasmic phase, which was confirmed by repeat activity at 120 and 180 minutes. When I switched on TV to a familiar news announcer, I thought that he had a cold because his voice sounded lower than normal, and throaty. Later I picked up a phone to call a friend and both the dial tone and the touch-tones sounded very unusual. Music at this point sounded normal, but I am sure that some tonal perception was altered by this drug. The effects seemed almost gone by 4 hours and were undetectable by 5 hours. Appetite seemed unaffected throughout, and dinner at the 5-hour point was very good. No GI problems occurred, and there were no after effects the next day."

(with 90 mg, orally) "The entire body was becoming activated (in a good way) but not much going on in the head. I am mentally clear but with the entire touch system a bit more activated than I would choose. This peaked at 3 hours, and was gone in another 3 hours. Everything is tactile."

(with 120 mg, orally) "There is as much to be said for what didn't happen as for what did. No visual changes. No cloudiness of the thought processes. No motor impairment what-so-ever. There was some down-shifting of music, with some distortion, which was overall more annoying than interesting. But I am glad I am alone because I cannot wear clothing. Anything touching the skin makes all my hair stand on end. The erection of my nipples is almost painful. Exploring sexual stimulation seemed a little dangerous but explored anyway. The climax was disappointing. Too much activity of a slightly scary sort. Never again at this level.

EXTENSIONS AND COMMENTARY: How does one classify this kind of compound? It doesn't seem to be a psychedelic, at least at the levels reported. A stimulant? There were no mentions made of any increase in cardiovascular activity. It sounds like an example of a tactile stimulant, not for treatment of impotence but with the potential of augmenting and enhancing sexual pleasure.

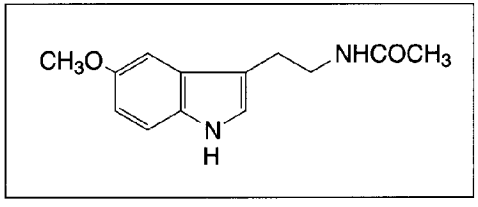
From the structure activity point of view, it seems that the methyl group on the indolic 2-position again allows oral activity of something that, without it, would not be. Here, the parent compound is DMT, and the other examples were

2-Me-DET and 5-MeO-TMT. But of these, 2-Me-DMT seems to be the most free of "negative" side-effects, except for the sound distortion (and as for the sexual stimulation, there might be an occasional shaker manqué amongst us who would consider that also as a negative).

#35. MELATONIN; TRYPTAMINE, N-ACETYL-5-METHOXY; INDOLE, 3-(2-ACETAMIDOETHYL)-5-METHOXY; SEROTONIN, N-ACETYL-O-METHYL; ACETAMIDE, N-[2-(5-METHOXYINDOL-3-YL)ETHYL]; N-ACETYL-5-METHOXYTRYPTAMINE; 3-(2-ACETAMIDOETHYL)-5-METHOXYINDOLE; N-ACETYL-O-METHYLSEROTONIN; N-[2-(5-METHOXYINDOL-3-YL)-ETHYL]ACETAMIDE; REGULIN

SYNTHESIS: To a well-stirred solution of 10 g 5-methoxyindole in 150 mL anhydrous Et_2O there was added, dropwise over the course of 30 min, a solution of 11 g oxalyl chloride in 150 mL anhydrous Et_2O. Stirring was continued for an additional 15 min during which time there was the separation of 5-methoxyindol-3-ylglyoxyl chloride as a tomato-red solid. This intermediate was removed by filtration, and used directly in the following step. To 40 mL of concentrated NH_4OH, which was being vigorously stirred, there was added as a solid, a bit at a time, the above glyoxyl chloride. This red solid gradually became yellow. After 15 min, there was added 200 mL 1 N HCl and the stirring continued, with the mechanical breaking-up of lumps, until the product was loose and finely dispersed. This was removed by filtration and washed with H_2O. After drying, this crude isolate weighed 8.2 g (55%) and was recrystallized twice from EtOH. The product, 5-methoxy-3-indolylglyoxylamide, was a fine, white crystalline material and had a mp of 245-247 °C.

To a well-stirred, warm suspension of 6.0 g LAH in 100 mL anhydrous dioxane, there was added a warm solution of 3.2 g of 5-methoxy-3-indolylglyoxylamide in 100 mL of anhydrous THF. The mixture was held at reflux for 38 h, cooled, and the excess hydride decomposed by the sequential addition of wet dioxane followed by 10 mL 5% aqueous NaOH. The resulting solids were removed by filtration, and extracted several times with boiling dioxane. The filtrate and washings were combined, dried over solid KOH, and stripped of solvent under vacuum, yielding an oily residue. This was dissolved in



80 mL warm benzene, decolorized with charcoal, and the filtered solution treated with an anhydrous solution of HCl in EtOH until it was acidic. The precipitate that formed weighed, after air drying, 1.1 g (29%) with mp 230-235 °C. This solid was recrystallized from EtOH, which provided the product 5-methoxytryptamine-hydrochloride with a melting point of 247.5-248.5 °C. Treatment with aqueous NaOH, followed by the extraction and isolation of the free base, provided a fine solid that could be recrystallized from $CHCl_3$ or EtOH, with a mp of 121-122 °C. This product has been obtained by two other procedures. The above starting indole, 5-methoxyindole, can be converted to the corresponding gramine with dimethylamine and formaldehyde, and this is converted easily with cyanide to the nitrile, 5-methoxy-3-indoleacetonitrile. This can be readily reduced to 5-methoxytryptamine with LAH. Another published procedure starts with the aldehyde of the indole, 5-methoxyindole-3-carboxaldehyde, which is coupled with nitromethane to form the nitrostyrene analogue, which has been reduced in turn to the above amine with LAH. In all cases, this intermediate amine was acetylated as described below.

To a solution of 0.2 g 5-methoxytryptamine in 4 mL of glacial HOAc there was added 2.0 mL acetic anhydride and heated at steam-bath temperature for 1 min. The volatiles were removed under vacuum and the residue was ground up under a mixture of EtOH and petroleum ether to yield 0.2 g (82%) of a white solid. This, after recrystallization from an ethanol/petroleum ether mixture, provided N-acetyl-5-methoxytryptamine (melatonin) as a white crystalline solid with a mp 116-118 °C. MS (in m/z): 173 (100%); indolemethylene$^+$ 160 (97%); parent ion 232 (28%). IR (in cm^{-1}): 713, 794, 825, 925, 1042, 1101, 1177.

DOSAGE: 1 - 10 mg, orally

DURATION: a few hours

QUALITATIVE COMMENTS: (with 2.5 mg, orally) "I took one tablet sublingually just before I lay down to sleep, and slept very well. I was not tired the next day."

(with 5 mg, orally) "I cannot distinguish it from placebo."

(with 10 mg, orally) "For over a month I would take 10 milligrams every night, or 5 or 2.5 milligrams. More 10's than 2.5's. I slept well and then I stopped it all, and still had no trouble sleeping. Why waste the money?"

EXTENSIONS AND COMMENTARY: This is a difficult drug to try to determine the active level. It is late. You want to sleep. You take a tab of melatonin and you sleep well. Or you don't take a tab of melatonin and still you sleep well. Or perhaps you sleep poorly — what connection can be drawn from the melatonin usage? The end-point of these studies is not the enhancement of consciousness but the loss of consciousness. I truly cannot say what the active level might be, because I do not

trans-Atlantic flights, rather than with the time-zone passage of trans-Atlantic or trans-Pacific flights? Personally I don't think so, as I don't get jet-lag (much) traveling in the Westerly direction, and I cross just as many time-zones and fly at similar altitudes. And I have not heard of jet-lag at all on North-to-South flights that may be just as long, but which do not cross many, if any, time zones. New York to Santiago, or London to Cape Town, for example.

This is all pharmacology. These are answers to the question, what does the drug do? A second point must be loudly mentioned here, one that concerns the questions, "How does it do what it does, and where does it go to do it?" Allow me to tell a tale based on an old, made up, Sufi legend.

The master asked the student, "How do you follow a guide who cannot be seen, who walks through a dark forest in the middle of the night?"

The student answers, "It is simple. Let him carry a light."

"But then," answers the teacher, "He is no longer the guide who cannot be seen."

"True, but at least I can now follow it, and I know where the light goes."

"You must be aware you are following a different guide?"

The student thinks for a minute, and then says, "Yes, of course I know that, but what else can I do?"

This is the sad plight of the research pharmacologist, who is trying to plot the in vivo course of a biochemical that cannot be followed. It must be labeled somehow, with a radioactive element, but nature demands that it is one that is not a normal part of its makeup. So he says, I would like to follow melatonin through the darkness of the body but I cannot see it as there is no light. I will attach a brilliant radioactive label to it, something like an iodine 125, so I can follow it as it goes here and there. The iodine is the light that the melatonin molecule is carrying, and the light can indeed be followed, but it is a different molecule. It is no longer melatonin; it is now 2-iodomelatonin. It is a completely different guide.

It is a sad story to tell, but this subtle shape-shifting is all too often invisible to the researcher. We will learn what melatonin does, by studying its radio-iodinated derivative. We will determine the quality of our synthetic analogues by measuring the displacement they make of iodinated melatonin from the melatonin receptor. Iodomelatonin is not melatonin. It is a different compound. It has a different biochemistry and a different pharmacology. It is used in melatonin studies only because it can be seen. Melatonin itself is, by its nature, a dark traveler in a dark forest, and we still do not know how to study it directly.

There is a third point, an additional fillip that is associated with the popular use of melatonin; the history of the transition of any interesting drug up the historic ladder, from availability to promotion, to broadcast usage, to spectacular claims, to prohibition, to illegality. This has always been seen as a pattern controlling drug use in our society. But will this apply to melatonin? We are midstride in this process, today. Its reputation as a sedative and life-extender within the health food store

circuit grew quickly in the early 90's. A sleep article in the magazine "Esquire" (Michael Segall, October, 1994) advanced the expected warning of not knowing enough about it. "Until more is known, though, it's probably not a good idea to self-medicate your jet lag with melatonin. No one knows how much you should take nor about the potential side effects." So far, right on schedule. Although a great deal is known, and potential side effects have been examined, the restrictive warning label must be voiced. But just recently, a feature article has appeared in another magazine ("Newsweek," August 7, 1995, by Geoffrey Cowley) that expands on its potential additional virtues, such as preventing pregnancy, boosting the immune system, preventing cancer, and extending life span. Heavy duty. It will be interesting to see if this precipitates an FDA control action in light of potential medical claims, or a DEA control action in light of an abuse potential. Maybe the sales of the chemical will have to hit something in the megatonage area first. I have just ordered a few grams from the Aldrich Chemical Company and I can state that its availability remains intact for the moment. But, if it is restricted, thus withdrawn and made illegal, its popularity will grow with renewed vigor, and it will be instructive to observe in just what way the dynamics of the illicit market will evolve!

This is a present day example of a problem in the making, one that law-makers and regulatory administrators have had to face again and again since that moment that the government decided it was necessary to make a pretense of controlling the relationship between its citizens and their drugs. In the name of drug control, melatonin will eventually become illegal, and it will then pass totally out of any semblance of control. The fact that it is a natural component of the healthy human body will probably carry little weight in any attempt to thwart its becoming outlawed. Compounds such as bufotenine and DMT are normal components of our nervous system, but they are currently Schedule I drugs due to their reputed abuse potential and the absence of any accepted medical use.

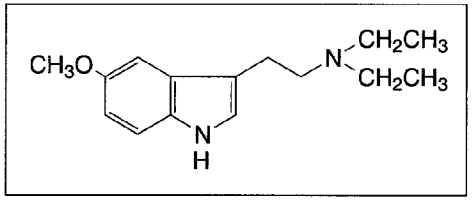
A few words are needed here concerning the neurotransmitter serotonin. It is the immediate precursor to melatonin in the brain, and it is the, no, **THE** neurotransmitter that is the sine qua non of the brain. Everything centers on it, everything is explained by it, and all virtue and all damage that occurs there is because of it. It is not a brain chemical from outside the body. If you swallow a bunch of it, it passes on through the body without making it to the brain, because it is too polar to get through what is called the "blood-brain barrier." But maybe an enabled precursor just might make it. Recently there has been a wide promotion of 5-hydroxytryptophan that just might play this role. If it were to be actively transported into the brain, it might produce cerebral serotonin. But maybe not. I am just a bit overwhelmed by the beneficial steroids that are not steroids, and the smart drug that may or may not make you smart, of the hormone substitutes that might or might not make you a sexy octogenarian. The over-the-counter world is awash with materials that appear to be virtuous but which are carefully presented as being without any medical claims. Back to serotonin. It is an essential factor in our brain

chemistry. Since it cannot be made elsewhere and be moved to where it is needed, it must be made on location. Most drugs are judged good or bad by their influence on the changes made of serotonin levels. This is the guide we follow because he is carrying the light. What is really happening in the brain is happening in darkness, because we have no way of seeing it.

It is my quiet hope that the psychedelic drugs will give us that guidance towards the understanding of the mind. They just might let us see that trail through the dark forest where most of the people who search choose to follow the lighted path.

#36. 5-MeO-DET; TRYPTAMINE, N,N-DIETHYL-5-METHOXY; INDOLE, 3-[2-(DIETHYLAMINO)ETHYL]-5-METHOXY; N,N-DIETHYL-5-METHOXYTRYPTAMINE; 3-[2-(DIETHYLAMINO)ETHYL]-5-METHOXYINDOLE

SYNTHESIS: (from 5-methoxytryptamine) A solution of 0.95 g of free-base 5-methoxytryptamine was dissolved in 10 mL warm IPA and, after returning to room temperature, treated first with 2.8 mL diisopropylethylamine followed by 1.2 mL bromoethane. After 3 days, TLC showed considerable starting material, so there was added an additional 2.8 g of the amine and 1.2 g of the bromide and the room-temperature stirring continued for an additional 3 days. The volatiles were removed under vacuum, and the residue treated with 1.6 g acetic anhydride, and heated on the steam bath for 20 min. The excess anhydride was destroyed by the addition of 3 mL concentrated NH_4OH, followed by dilution with 100 mL 0.5 N H_2SO_4. The aqueous phase was washed with 3x50 mL CH_2Cl_2, made basic with 6N NaOH and extracted with 3x25 mL CH_2Cl_2. The solvent from the pooled extracts was removed under vacuum, and the residue distilled at the KugelRohr.



A fraction boiling at 190-200 °C at 0.5 mm/Hg providing 0.45 g of a white oil. This was dissolved in 2.5 mL IPA, acidified with approximately 8 drops of concentrated HCl, which produced spontaneous crystallization. There was added, slowly and with good stirring, 20 mL of anhydrous Et_2O to yield beautiful white crystals of N,N-diethyl-5-methoxytryptamine hydrochloride (5-MeO-DET), weighing 0.50 g (35%) and with a mp 190-191 °C. IR (in cm^{-1}): 817, 830, 930, 1109, 1185. MS (in m/z): $C_5H_{12}N^+$ 86 (100%), $C_3H_8N^+$ 58 (12%); indolemethylene$^+$ 160 (4%); parent ion 246 (2%).

The pooled extracts of the CH_2Cl_2 washings of the acidified aqueous phase above gave, upon removal of the solvent under vacuum, a brownish residue that crystallized. Recrystallization of this from MeOH gave 0.44 g of N-ethylmelatonin as a white crystalline solid. IR (in cm^{-1}): 790, 829, 929, 1031, 1068,1108, 1182, 1199. MS (in m/z): 173 (100%); indolemethylene$^+$ 160 (67%); parent ion 260 (14%). This amide proved extremely difficult to hydrolyze.

(from 5-methoxyindole) To a well-stirred solution of 1.5 g 5-methoxyindole in 15 mL anhydrous Et_2O there was added, dropwise over the course of 30 min, a solution of 1.4 g oxalyl chloride in 15 mL anhydrous Et_2O. Stirring was continued for an additional 15 min, during which time there was the separation of 5-methoxyindol-3-ylglyoxyl chloride as a red crystalline solid. This intermediate was removed by filtration and washed with Et_2O, and was used directly in the following step. This was added in small dabs to 2.0 g anhydrous diethylamine, cooled and well-stirred. The off-white resulting solids were suspended in 100 mL 1 N HCl, stirred until it was a loose and creamy texture, then filtered and washed with H_2O. Recrystallization from acetonitrile gave 2.24 g (80%) N,N-diethyl-5-methoxyindol-3-ylglyoxylamide as white solids, with a mp of 158-160 °C.

A solution of 2.1 g N,N-diethyl-5-methoxyindol-3-ylglyoxylamide in 35 mL anhydrous THF was added, slowly, to 3.2 g LAH in 60 mL THF which was well-stirred and held at reflux temperature under an inert atmosphere. After the addition was complete, reflux was maintained for an additional 16 h, the reaction mixture cooled, and the excess hydride destroyed by the cautious addition of wet THF. Aqueous 15% NaOH was added cautiously until the solids had a loose, white cottage cheese character to them, and the mobile phase tested basic by external damp pH paper. These solids were removed by filtration, washed with first THF and then with MeOH. The filtrate and washings were combined, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum. The residue was distilled, yielding a fraction boiling at 190-200 °C at 0.5 mm/Hg that weighed 1.45 g and was a white oil. This was dissolved in 8 mL IPA, acidified with concentrated HCl until it was acidic to external damp pH paper, and diluted with Et_2O and stirred until crystallization appeared to be complete. N,N-diethyl-5-methoxytryptamine hydrochloride (5-MeO-DET) was obtained as white crystals, weighing 1.60 g (74%).

DOSAGE: 1 - 3 mg, orally

DURATION: 3 - 4 h

QUALITATIVE COMMENTS: (with 2 mg, orally) "My tinnitus is really out there, and there is no way of getting away from it. Light-headed in a funny way — no hypotension, not dizzy — maybe something to do with the inner ear? It is in the head, I am attentive, and I am not comfortable. Three hours into it I am down, and I have a bit of wine, and I am aware of it. Am I drunk? Was I drunk earlier? I was intoxicated, to be sure."

(with 3 mg, orally) "It hit in a half hour, and the thought that came to mind was the phrase from my days at college, "Boy, I really felt that drink!" I may be sloppy, but let me explore the sexual. Wow. I may be spacey in the head, but my body knows where it is at. The next day was normal. I don't think I want to do this again."

(with 3 mg, orally) "Effect felt within 20 mins, mainly light-headedness, almost dizziness. This blocked anything else. Just wanted to stay quiet and hope it would all go away as soon as possible. During the next hour, lying beside husband (who was experiencing the same effect but not minding it as much), I became aware of another dimension behind the dizziness. I could sense enough of it to believe that it would have been interesting to explore, but that there was no way to get through the dizzies, which effectively blocked anything else. At approximately the hour and a half to two hour point, I felt a faint lessening of the head-fuzzies, and tested it out by walking to the living room. Felt it necessary to walk carefully. Body felt heavy and mood was rather dark, verging on depressed. After that, attempted love-making, which was extraordinarily successful for husband. For myself, there was still a reluctance to let down my guard. My back problems had been bothering me quite a bit, during all of this, and even two Bufferins didn't help as much as I would have liked. It's quite obvious that, if it were possible to remove the part of the molecule that causes the dizzies, this would be one of the best drugs for erotic stuff imaginable. And if wishes were horses, etc. Too bad. Would I try this again? And at a higher dosage? No, and No. "

(10 mg, smoked with peppermint leaves) "After a few minutes a high feeling with some dizziness, intense heartbeat, trembling, anxiety, restlessness, cold sweating, paleness and weak belly cramps. There were some visions I could not concentrate on because of the strong side-effects. I felt sick, went to bed, and was very glad when the effects disappeared after about one and a half hours."

EXTENSIONS AND COMMENTARY: The is one of the most provocative temptresses I have ever encountered in the tryptamine world. It is a case of having a protégé that you absolutely know will be a success if allowed to come to fulfillment, and yet you know that uncontrolled circumstances will prevent that fulfillment.

Here is a simple, easy to make compound that lies in-between the lower homologue, 5-MeO-DMT (active at 10+ milligrams by any parenteral route) and 5-MeO-DIPT (active at 10+ milligrams orally). The most rudimentary logic demands, yea, screams, that 5-MeO-DET should be active at 10+ milligrams, probably also by the oral route. That is the clear potential of this individual. But, at a fraction of this dosage, an unexpected new property is apparent, one that suggests neurotoxicity, and thus will preclude the achievement of that 10 milligram psychedelic potential. There is a light-headedness, a vertigo and intoxication, a warning of fragility, that pretty effectively blocks any exploration into areas that

might be psychologically virtuous. This is reinforced by a report I had received from a person who had smoked some 10 milligrams of it. His report is in the qualitative comments above. He described it as a "torture psychedelic."

This is a new and totally unexpected negative activity that may well be unique to this particular diethyl material — it certainly was not reported with either of the immediate homologues, the dimethyl or the diisopropyl. And, as an intriguing corollary, could the unexpected new activity property that brought the physical concern also be the thing that brought the terrific erotic enhancement? Are they tied together as a single new component of action? Or might there be two new components of action, the scary vertigo and the friendly sexual?

To me, an obvious bridge to help explain this seeming discontinuity would be the dipropyl analogue. I made the compound, and explored it up to its active levels. It is an easy compound to make, and has been known in the scientific literature for many years. My quandary was how to present it in this book. Should I make it a recipe in its own rights, giving the detailed synthesis and a formal position as an active tryptamine? Its actions are ambiguous, and not totally positive, making an argument for its inclusion as a footnote in some other, more interesting recipe. It is this latter route that I have chosen, so here is the 5-MeO-DPT story, both chemical and pharmacological, tucked away in the bigger 5-MeO-DET

CHEMISTRY: To a warm solution of 0.9 g 5-methoxytryptamine in 10 mL IPA there was added 2.8 mL diisopropylethylamine and 1.5 mL propyl iodide, and the mixture was heated on the steam bath for 5 h. TLC analysis at this time showed the presence of both the mono- and the dialkylamines, but there was no indication of the presence of unreacted 5-methoxytryptamine or of the quaternary salt. After removal of the volatiles under vacuum, a CH_2Cl_2 solution of the residue was treated with 1 g acetic anhydride (on the steam bath for 5 min) followed by 2 mL ammonium hydroxide. Extraction of this solution with 1 N H_2SO_4 proved to be almost worthless, as the extracts after separation, alkalinification with 6 N NaOH, extraction with CH_2Cl_2 and distillation of the residues following removal of the solvent, provided only a few milligrams of the desired product. The product had remained in the CH_2Cl_2. The solvent was removed under vacuum, and the residue partitioned between MeOH (containing a small amount of aqueous NaOH) and hexane. The hexane fraction was concentrated under vacuum to provide 0.54 g of an almost colorless oil which was distilled by KugelRohr. A white oil was obtained, boiling at 170-180 °C at 0.04 mm/Hg, which weighed 0.49 g. This was dissolved in 2.5 mL IPA and neutralized with 8 drops of concentrated HCl. The solution was diluted with 25 mL anhydrous Et_2O to provide 5-methoxy-N,N-dipropyltryptamine hydrochloride as a white crystalline salt. This was removed by filtration, washed with Et_2O, air dried to constant weight, and weighed 0.54 g. The mp was 193-194 °C. IR (in cm^{-1}): 811, 828, 929, 1079, 1103, 1186. MS (in m/z): $C_7H_{16}N^+$ 114 (100%); methoxyindolemethylene$^+$ 160 (13%); parent ion 274 (3%).

QUALITATIVE COMMENTS: (with 4.0 mg, orally) "Within the hour there is something and after another hour there is nothing. Happy to go on up."

(with 6.0 mg, orally) "I am up above baseline for sure. Maybe to a ++, erotic maybe, and not too much light-headedness. It is comfortable. Completely out before the fourth hour."

(with 8.4 mg, orally) "Aware in 12 minutes, some head noises at 20 minutes. These noises are reminiscent of the 5-MeO-DET in that they were "bells" which were bad and the underlying "turn-on" which was good. But the "bells" were outweighing the "turn-on." Let's ride it out but then, for that matter, what choice is there! At the 25 minute point the turn-on now outweighs the bell noise. But these keep alternating. Pulse 84; no cardiovascular. But for the next half hour, the bells > the turn-on. At three hours, almost baseline, and I eat modestly. I have better things to do with my time."

There is the irrepressible fascination of this type of research. Could one tinker with the molecule to emphasize one new property and de-emphasize another? Here is the theoretical conundrum stripped of arcane chemical words and put into non-technical symbolism. Give a single letter to a substitution group, increasing as the group increases in size. Here is the code:

A = hydrogen
B = methyl
C = ethyl
D = propyl
E = isopropyl
F = butyl
G = s-butyl

And let's arrange the 5-methoxylated tryptamines in order of increasing mass, and see if there is a pattern apparent as to the quantity or quality of action.

A	A	5-MeO-T	anti-radiation, not a psychedelic	?
A	B	5-MeO-NMT	unknown activity	?
B	B	5-MeO-DMT,	positive, psychedelic, out-of-body	6-20 mg
B	E	5-MeO-MIPT	mixed, complex	4-6 mg
C	C	5-MeO-DET	negative, vertigo, erotic	2-3 mg
C—	C	5-MeO-pyr-T	very negative, amnesia	0.5-2 mg
D	D	5-MeO-DPT	neutral, balance, good and bad	6-10 mg
E	E	5-MeO-DIPT	positive, LSD-like psychedelic	8-12 mg
F	F	5-MeO-DBT	known compound, unknown activity	?
G	G	5-MeO-DSBT	unknown compound	-

So, I ask, how could C C be modified to eliminate the vertigo component, maintain the erotic component, perhaps even maintain the psychedelic component, and certainly maintain the orally active property? Clearly, tying them together in the form of a pyrrolidine ring didn't do it. Only one of these listed 5-methoxy's of known activity is asymmetric, the methyl isopropyl analogue. It is probably through this device of mixing and comparing that our answer will be found. Some guide might come from the 5-hydrogen counterparts, more of which have been explored in man. The variations with a constant isopropyl group have been organized in the recipe for EIPT. Here is the rest of the story.

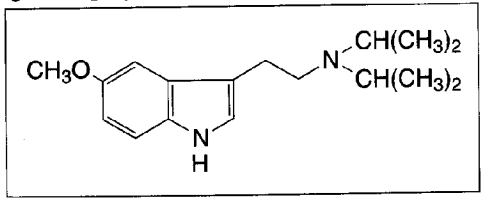
B	C	MET	positive, psychedelic	80-100 mg
B	D	MPT	unknown	> 50 mg
B	E	MIPT	mixed, complex	10-25 mg
B	F	MBT	mixed	250-400 mg
B	G	MSBT	unknown	?
C	E	EIPT	mixed	24-40 mg

My hope is that getting leads from the second list (no substituent at the indolic 5-position) could help guide the choice of asymmetric substituents for the first list (a methoxy group at the 5-position) that would lead to an expected increase in potency but to an unexpected change in quality of action.

Kierkegaard probably summed it up best. "Life is not a problem to be solved, it is a mystery to be lived." That's chemistry, friends; that's life!

#37. 5-MeO-DIPT; TRYPTAMINE, N,N-DIISOPROPYL-5-METHOXY; INDOLE, 3-[2-(DIISOPROPYLAMINO)ETHYL]-5-METHOXY; N,N-DIISOPROPYL-5-METHOXYTRYPTAMINE; 3-[2-(DIISOPROPYL-AMINO)ETHYL]-5-METHOXYINDOLE

SYNTHESIS: To a solution of 3.0 g 5-methoxytryptamine (see under melatonin for its preparation) in 20 mL sulfolane (tetramethylenesulfone) there was added 8.2 g diisopropylethyl amine and 10.7 g 2-iodopropane, and the two-phase mixture was heated on the steam bath with frequent shaking. After 3 h, the mixture was brought back to room temperature and stirred vigorously for an additional 16 h. After the removal of all volatiles under vacuum, the residue (30 g) was diluted with 100 mL H_2O, which gave a clear solution. The addition of 10 mL 5% aqueous NaOH produced a cloudy suspension that was extracted with



3x40 mL hexane. These pooled extracts were stripped of solvent to yield 1.0 g of an almost colorless oil that was distilled at the KugelRohr. A small cut at 100 °C (at 0.01 mm/Hg) proved to be largely residual sulfolane (about 0.01 g) and the bulk of the product distilled at 140-150 °C to give a viscous white oil, 0.80 g. This was dissolved in 3.5 mL IPA and neutralized with 15 drops of concentrated HCl. The addition of five drops of anhydrous Et_2O instigated crystallization, and the product was removed by filtration, washed with 4:1 IPA/Et_2O mixture, and air-dried. There was thus obtained 0.85 g of a fine white crystalline product, N,N-diisopropyl-5-methoxytryptamine hydrochloride (5-MeO-DIPT), with a mp 181-182 °C (17%). IR (in cm^{-1}): 731, 809, 826, 931, 1035, 1064, with an NH at 3165. MS (in m/z): $C_7H_{16}N^+$ 114 (100%); $C_4H_{10}N^+$ 72 (31%); indolemethylene$^+$ 160 (12%); parent ion 274 (<1%). There was no detectable 5-MeO-NIPT by GC (<1%).

DOSAGE: 6 - 12 mg, orally

DURATION: 4 - 8 h

QUALITATIVE COMMENTS: (with 6 mg, orally) "Effects were present in twenty minutes, and I took my portable radio into the garden at forty minutes just to pull weeds. Each weed had special significance, and my cat joined me and agreed with me. This is excessively strange. The radio was discussing a President Ford fund-raiser, and continued with word sequences such as fund, fun, profun, profound, profane, refrain, and on and on. A car drove by with sitar music playing on its radio! Why not. And by my hour number three, I am back where I started. That was quite a morning."

(with 6 mg, orally) "Talking wasn't really interesting, music wasn't interesting, nothing was very interesting. One hour in and I felt turned on as if a wave passed over my body, and then the wave went back to the ocean, or wherever waves go. I was getting hungry but I didn't want to go to the kitchen, as I didn't want to interact with anyone I might encounter. What remained with me the longest was the awareness of vibrations, and what felt best was the stillness. Was back to baseline in 4 hours."

(with 7 mg, orally) "In one hour I was in a marvelous, sexy place. Everything was shaded with eroticism. Sex was explosive, and in another three hours I was completely ready for the outside, public world. As a short term aphrodisiac, this leaves 2C-B in the dust."

(with 10 mg, orally) "Colors on the edges of the wiggles of the eye, a sort of Jessie Allen running design with color contrasts and sparkle. People's faces were interesting, quite serious, and not completely friendly. Well after everything had cleared, later in the evening, there was a residual, good clean feeling. This is a definite sense-distorter. I am not completely sure I like it."

(with 10 mg, orally) "We found it to be outstanding — combining the best characteristics of two other like products while contributing a penetrating efficaciousness of its own."

(with 12 mg, orally) "Had prepared for this experience during the day, and was looking forward to the time with my partner. Flowers, candles, fluffy pillows, arranged for food, etc. Large pillar-type candles and the glow was nice and warm. Warm was comfort and comfort was good. Warm led into a wonderful sexual turn-on, where my entire body was alive and alert. This was one hour into the trip. This sexual turn-on was the feeling of a bud about to unfold into a full-blown, beautiful flower, which happened during love-making. The flower continued to fill out fuller and fuller for a couple of hours, and then just remained a full-blown, beautiful, wonderful flower, and I fell asleep with this feeling."

(with 12 mg, orally) "Remembering how hungry I got during my last 6 mg. experience, and without any dietary restriction, I ate a vegetarian burrito four hours earlier. It took an hour for me to turn on. I have never experienced such an increase of the peristalsis process in moving the burrito through my colon and with each defecation I would become a little more turned on. As I became more turned on, the greater I felt the sense of hypertension. A mind/body load became uncomfortable. It was never psychedelic in the way of acid or psilocybe. My muscles, gluteus maximus, the lateral rotators that connect to the trochanter and the large muscles that connect to the hamstrings, all contracted and spasmed. Psychologically it was as though my conservative instinct, my sense of Being, became extremely agitated. I felt completely unnerved, and the only relief offered was by having sex. As the effects of this material were rather extreme, I never felt as though I was having a psychedelic experience. Maybe because it was all about dealing with body load and discomfort."

(with 12 mg, orally) "There was a very strange, almost paranoid session of listening to music, about an hour and a half into it. The program was a program of Irish music called "The Thistle and Shamrock," but I had paid no attention to the announcement. What was being played were three nativity pieces with song and words, from strange places. What I heard were three distant, fraudulent selections with generically meaningless words, mumbled so as to sound authentic. Everything was faked. It was "Hearts of Space" music in the worst possible taste. My neutral observer was completely taken in by it all, and quite enjoyed it. It turned out that I was wrong; the music was strange but of good quality. It was my interpretation that was screwed up."

(with 12 mg, orally) "My experience with this material was different in its action than anything I had tried in the past — it came on quicker but with much less intensity. I really enjoyed the mellowness, and it sort of waved in and out. I came down after almost an hour, smoked a little marijuana, and went back up to where I had been previously. I could do this around my children, and they would know I was happy but I doubt they would realize just exactly what was up. I liked it and would consider a public event (craft fair, street fair, window shopping) very adventurous.

No hangover; sleep excellent."

(with 12 mg, orally) "Awful, awful taste. Quickly aware and in the second half hour I rapidly shot up to a +++ in a very LSD-like manner, without the visuals. Time was quite slowed down during this come-on. Erotic world was fantastic, explosive, almost scary. Rapid drop-off, and by the fourth hour I am clear of any effects."

EXTENSIONS AND COMMENTARY: Here is a rather fast-acting psychedelic-like drug, with suggestions of LSD action but with essential differences. It has a lot of things going for it. It is short-lived, a virtue in many people's minds. It may vie with 2C-B as a potential aphrodisiac. It is reasonably easy to synthesize. It is of a pretty high potency. The physical side-effects are minimal. These are the positive points.

But there are points that are neutral or actually negative, and they must be considered. A fair number of people who have explored 5-MeO-DIPT have said that there are some uncomfortable aspects with the experience. Not only are there few if any visual enhancements, but the altered state they entered was one that they simply couldn't use. They couldn't make intuitive leaps. They were wasting their time.

On the neutral, but scientifically exciting edge, there is again some musical sound distortions that remind one of the actions of the analogue without the 5-methoxy group, DIPT. With DIPT, there was a physical, harmonic distortion of the sounds that were heard. With 5-MeO-DIPT (again, two isopropyl groups on the basic nitrogen) these perversions involved musical character and interpretation. None of the comments suggested harmonic structure. I do believe that these two drugs, having such an intimate structural resemblance but with their different distortions of music interpretation, would be rewarding to explore more fully with the view of objectively defining these changes. 5-MeO-DIPT is a mixed bag. But it is a bag that I predict will demand a great deal of interest sometime in the future, especially if the erotic enhancement at a low dose proves to be a consistent property.

There is an interesting story associated with the first publication of the chemistry and pharmacology of this compound, in 1981. My co-author was a Michael Carter, in England. We had discussed a number of potentially interesting tryptamines and agreed upon making a small handful to evaluate. We had, some six years earlier, co-published a paper describing a new and exciting phenethylamine which we called 2C-B, and we expected to work together, in our separate labs, on a number of research projects. And indeed, I heard from Michael from a new address, and he sent me his samples and reports of the new compounds we had decided to make, including 5-MeO-DIPT. Our synthetic materials were spectroscopically identical and the human trials had shown that they were very similar. Along with the samples and a letter there came the draft of a possible paper. I wrote back to Michael my own version of the paper, to his new address, and the letter was

returned as undeliverable — no forwarding address available! Again I sent it back, with full first-class postage and a clear request to forward it if necessary — and this time it simply never came back at all.

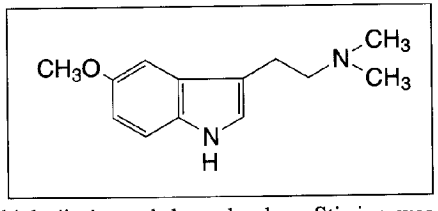
The issue sat there for a year or two, and I hoped that something would occur. Nothing. I finally wrote to the telephone company in London (Michael had said something about eventually moving up to London) and asked if they could possibly send me the addresses of all the Michael F. Carter that had telephone service in the greater London area. Bless their hearts, they sent back a list of twenty names. And a statement that they were appreciative of having the middle initial, as without that the list would have been in the hundreds.

I wrote to each and every one of these Michael F. Carter's the same letter phrased in a way that required no answer if it was the wrong person, but which would inspire immediate answer from the right Michael F. Carter's. No answer. Was he alive? Could some unthinkable thing have happened to him associated with his drug experimentation, either personally or legally? There was absolutely no way to tell, so Michael, somewhere out there, if you read this please drop me a note if you wish to and are able to.

So I left the paper pretty much with his ideas in it, crossed my fingers as I used my address for both authors, and sent it off for publication. The paper appeared and I sincerely hope that I did the right thing.

#38. 5-MeO-DMT; TRYPTAMINE, 5-METHOXY-N,N-DIMETHYL; INDOLE, 5-METHOXY-3-[2-(DIMETHYLAMINO)ETHYL]; 5-METHOXY-N,N-DIMETHYLTRYPTAMINE; 5-METHOXY-3-[2-(DIMETHYLAMINO)ETHYL]INDOLE; N,N,O-TRIMETHYLSEROTONIN; N,N,O-TMS; BUFOTENINE METHYL ETHER; O-METHYLBUFOTENINE; OMB

SYNTHESIS: To a cooled and well-stirred solution of 16 g 5-methoxyindole in 200 mL anhydrous Et_2O there was added, dropwise, 25 g oxalyl chloride. Stirring continued for an additional 10 min, then the red solids were removed by filtration, washed lightly with Et_2O, and returned to the reaction beaker as a suspension in 200 mL fresh anhydrous Et_2O. To this there was added a solution of 8.5 g dimethylamine in 25 mL anhydrous Et_2O which discharged the red color. Stirring was continued for an additional 0.5 h, and the solids were removed by filtration and



washed with Et_2O. These were suspended in H_2O, filtered, and washed alternately with H_2O and Et_2O. Recrystallization from THF/Et_2O provided 20 g (75%) 5-methoxy-N,N-dimethylindol-3-ylglyoxylamide, mp 223-223.5 °C, as fine white crystals.

To a well-stirred suspension of 11.7 g LAH in 350 mL anhydrous Et_2O there was added, in small portions, a suspension of 18.5 g 5-methoxy-N,N-dimethylindol-3-ylglyoxylamide in 200 mL hot benzene. The last of the solids were rinsed out with anhydrous Et_2O and the mixture held at reflux for 1.5 h. After cooling with an external ice bath, the reaction complex and excess hydride were decomposed by the cautious addition of H_2O. The inorganic solids were removed by filtration, the filter cake washed with additional Et_2O, the filtrate and washing were combined and dried over anhydrous $MgSO_4$, and the solvents removed under vacuum. The residue was distilled at the KugelRohr to provide a colorless fraction, distilling at 160-170 °C at 0.6 mm/Hg, that crystallized on cooling. There was thus obtained 12.8 g (78%) 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) which on recrystallization from hexane, had a mp 69-70 °C. The hydrochloride salt can be made by passing a stream of hydrogen chloride gas through an Et_2O solution of the base. It, upon recrystallization from EtOH/Et_2O, had a mp of 145-146 °C.

DOSAGE: 6 - 20 mg, smoked; 2 - 3 mg, i.v.

DURATION: 1 - 2 h

QUALITATIVE COMMENTS: (with 6 mg, smoked) "I felt it in a minute — not really light head, but the head feels close to the lower parts of the body — close to the ground — knees weak — distinct shakes. I peaked at 2 or three minutes. It was quite intense, but not the max of DMT at 30 milligrams and no sensory close-out. Slight nausea on the drop-off — I am glad I had not eaten anything. Overall comparison to DMT, more potent, slightly faster, but like DMT is largely a simple, stoning drug with no sensory contribution, no intellectual contribution. It's greatest contribution might be to provide a subject the vocabulary of an altered state of consciousness so that, with interesting and constructive drugs, these effects will be familiar, and thus not distractions."

(with 8 mg, smoked) "I was blown away, far away I might add, but only for 10 minutes and effects were gone by half an hour. During this episode mental activity was almost absent. I can't say I wasn't 'impressed' in some way, though it wasn't exactly what I expected. I had read reports with statements varying from 'dwarfs + elves' to 'conk on the head,' the latter of which relates more closely to my experience."

(with perhaps 10 mg, smoked) "Onset was gentle, perhaps over 15 minutes. I felt like all of my blood had turned to concrete. There were no noticeable visual effects, but my hearing was slightly diminished. The whole experience was over after 1 hour."

(with perhaps 15 mg, smoked) "I took a hit from the pipe with five-methoxy in it, and after the 8 to 10 seconds it took to carry the chemical to my brain I remember starting to fall over from my sitting position. My normal physical perceptions dissolved away from my awareness. My ears started to ring and I started to float off. I was acutely aware of a certain resonation of my aural perception, an electrical buzzing that fluctuated in synch with my visual perception. What I saw can only be described as a fantastically subtle multicolored phosphene, completely filling every area visually available. I say it in this way because I was simultaneously losing contact with my body, I could not tell if my eyes were open or shut, although I initially had the feeling that they were darting back and forth, from side to side. These feelings and sensations built up in intensity very quickly, a matter of seconds: I can remember this feeling of building intensity up to a point, and then I was not there in my body or in time. In the 10 to 15 minutes that my body was under the influence of the drug my mind was completely referenceless, there was no way for my consciousness to limit or gauge the stimuli my being was barraged with. I remember switching to a perception where the endless and intricate phosphene was love and the energy of light. I called upon those forces within my being to realign and submit, to let go of all the cogent fears and just exist ... and that innate decision saved me a lot of psychic damage. What is most outstanding about the way it feels is an inability to judge in any way, by any method of the mind ... it is unconquerable, as deep and profound as a totally unconditional love that is life. What a trip, huh?"

(with 15 mg, smoked) "At about 60 seconds after I smoked this free-base, I beheld every thought that was going on everywhere in the universe and all possible realities while I was wracked out with this horrible ruthless love. It scared the hell out of me. When I could see again (15 minutes later) it was almost as if there was an echo of a thought in my head saying that I was given an extremely rare look at the true consciousness of it all. I've never been hit this hard since then. A definite ++++."

(with perhaps 20 mg, smoked) "This is a very strong hallucinogen. A twenty minute experience. For me it was like adding the MDMA experience to DMT. DMT for me is terrifying (I still go back though) and I must really think about it before proceeding. The 5-MeO-DMT was much more relaxed, a kind of cosmic consciousness type of experience. I broke into a space similar to DMT but it was more like receiving grace. I felt a little shaky (tremor-like) coming down."

(with 25 mg, smoked) "I placed 25 mg of 5-methoxy-DMT in a stainless steel one-quarter teaspoon and vaporized it over a cigarette lighter collecting the smoke in an upside-down funnel. All smoke was inhaled; the taste was mild — none of the plastic taste of DMT. About 10 seconds or so after inhaling the last of the smoke, it began with a fast-rising sense of excitement and wonder, with an undertone of "Now you've done it," but dominated by a sense of, "WOW, This Is IT!" There was a tremendous sense of speed and acceleration. In perhaps 10 more seconds these feelings built to an intensity I had never experienced before. The *entire universe* imploded through my consciousness. It's as if the mind is capable

of experiencing a very large number of objects, situations and feelings, but normally perceives them only one at a time. I felt that my mind was perceiving them all at once. There was no distance, no possibility of examining the experience. This was simply the most intense experience possible; a singularity, a white-out (as opposed to a black out). I have little memory of the state itself. I have no memory, for example, of whether my eyes were opened or closed. After some seconds or minutes, it started to fade and came to resemble a merely intense psychedelic state. Here I had the feeling, a visualization of being part of the universe of beings, all active in our daily, interwoven tasks, still moving at an incredible rate, and with a longing for a single group/organism awareness and transcendence. In a few more minutes it faded to an alert (+ one) state with an additional sense of awe and wonder, relief, and a strong feeling of gratitude toward the universe in general, for the experience."

(with 30 mg, smoking) "I placed approx. 30 mg of 5-MeO into a pipe, and smoked it, in one toke, without a second thought. An instant later, I was crawled up on my bed (in the fetal position) with my eyes closed, squirming around, screaming (in my head) 'Fuck! You killed yourself!' I repeated this several times, very fearful of death. I didn't see anything, while my eyes were shut, except for a bright white light, that which you see after staring at a bright light. The only other "vision" was one in my mind -- I came to the realization that my life would be wasted if I died there. This showed me all of my scripts being discarded and nothing good happening ever again. It was a glimpse into my future, if I died. I concentrated on breathing and that helped me survive (mentally). I walked into the living room and placed a CD into the stereo, and as the first song started, my attention span disappeared, and I walked back into my bedroom. To my surprise, forty minutes had passed, in what I remembered as mere seconds. This scared me, thinking that maybe I had blacked out. I felt the effect for about an hour, then it slowly faded away."

(with an unknown but large amount, smoked) "I observed the subject pass very quickly into an almost coma-like state. Within seconds his face became purple and his breathing stopped. I pounded his chest, and breathed for him, and he seemed to emerge in consciousness, with the comment, 'This is absolute ecstasy.' He stopped breathing a second time, and both heart massage and mouth-to-mouth resuscitation was provided. Again, he recovered and managed to maintain a continuing consciousness and achieve a partial recovery. In the awake condition he was increasingly lucid, but on closing his eyes he became possessed with what he called "The energy of terror." He could not sleep, as upon closing his eyes he felt threatened in a way he could not tolerate. Three days later, medical intervention with antipsychotic medication was provided, which allowed the recovery of an acceptable behavior pattern in a few more days."

(with 35 mg, orally): "No activity."

(with 0.25 mg, intravenously): "A real effect."

(with 0.5 mg, intravenously) "I felt the effects distinctly within a minute, along with some pain at the injection site. In a few minutes I felt a very distinct calming and stilling of my mind. While I could have carried on a conversation about anything and didn't feel the least bit stoned, I found the feeling very recognizable."

(with 0.7 mg, intravenously): "This was basically a +1 experience. After a few instances I felt its motion, very gentle waves. I was thinking about thinking about the experience, about writing about it, and so I was experiencing myself as both observer and editor. This was not overwhelming, but gentle."

(with 1.3 mg, intravenously) "In a few seconds I was participating in exquisite, full body, teeth-chattering shivers that lasted in all about 10 minutes, nearly the duration of the effects. The sensations seemed to come more from my head region, whereas my 'full blown' experiences of smoked 5-MeO-DMT seemed to emanate from my center and heart."

(with 2.3 mg, intravenously) "I remember having a perspective of knowing I was aware and, if not from the start of the experience then very soon into it, knowing I knew I was aware. I thought I was an ocean. I don't remember where I first lost continuity of consciousness (this is a little like a black-out from hard liquor) but I remember being aware of the sounds I was making apparently some time after I began vocalizing. Around the time I thought to change these sounds as I pleased, I also noted with brief wonder that the sound was continuous, not changed by my breathing. I sang my way back."

(with 3.1 mg, intravenously) "I vocalized effortlessly. I was getting in touch with my body. I said, 'Turn off the lights,' and 'I love you,' and then I lost it. I was amazed later to find a roomful of people who had been frightened by the noises they had been amazed to hear, and I was amazed to be told I had made."

EXTENSIONS AND COMMENTARY: This is, like DMT, another naturally occurring alkaloid that is not orally active. And, as with DMT, it is almost always smoked. This is the reason that both there and here, there are several entries with the word "perhaps" in the dosage statement. When the transportation vehicle is a rolled joint containing some inert plant carrier, or a glass pipe heated with a torch, who can accurately say how much of the drug was actually volatilized and drawn into the lungs? Further, from the qualitative range of responses, one can truly say, it is different things to different folks. I don't know of any active oral level (I have been told of it being tried at 35 milligrams) but a number of experiments with oral 5-MeO-DMT preceded by harmaline have shown activity in the 10 - 25 milligram area. These are discussed in the Hoasca vs. Ayahuasca chapter. Some trial i.v. experiments with radioactively labeled and unlabeled materials showed no effects at 100 micrograms, but real effects at 250 micrograms. Higher levels have convincingly established the enhanced potency that is the result of this route. The injection process is faster than the smoking process, and it avoids the smoke's odd flavor.

5-MeO-DMT was first observed in a member of the Rue family (Rutaceae)

called *Dictyoloma incanescens*. Now it is recognized as a major component of a number of South American snuffs. The snuff called cohoba is generally associated with plants of the *Piptadenia* and *Mimosa* genus, and as they are largely DMT-containing, they are discussed under that entry. But there are other snuffs, such as yakee and yato (in Colombia) and paricá, epená and nyakwana in Brazil, which should probably be discussed here. The plants used are of the *Virola* genus, containing trees most plentifully found in the Amazon basin.

There has been a long-standing and never-to-be-resolved disagreement amongst botanists as to the best way of classifying plants. There are the morphotaxonomists, who insist that species assignment should be based primarily on appearance, and there are the chemotaxonomists who feel that the natural composition should be a deciding factor in the distinction between species. But the ultimate requirement for morphology is to find the plant in bloom, and for chemistry, to have some analytical capabilities. Often, neither luxury is available in the jungles of the rain forest. A major contributor to the *Virola* snuffs, *Virola theiodora*, is a good case in point. Two plant sources, both gathered in Brazil, have been found to have radically different compositions. In one, 5-MeO-DMT is substantially the only alkaloid found in the bark, whereas in the other, DMT is the major alkaloid. But both have DMT almost exclusively in the young green shoots. Are they the same species? Another plant used in some of the snuff preparations is *Virola calophylla*, where the bark, root, leaves and shoots all run about 90% DMT as the alkaloid content. Yet, the alkaloids in the root and bark of *Virola rufula* consist of some 95% 5-MeO-DMT.

The inquiries into metabolic 6-hydroxylation as a prelude to biological activity have been made with both 5-MeO-DMT and the corresponding primary tryptamine (see below). 6-HO-5-MeO-DMT has been shown in several animal models to be pharmacologically less active than its parent compound. See the discussion under DET for the role that this metabolism played in some early clinical studies.

Removing one of the N-methyl groups provides N-methyl-5-methoxytryptamine (5-MeO-NMT), which has its own entry. Removal of both methyl groups from the nitrogen gives 5-methoxytryptamine (5-MeO-T) which has been explored most extensively by Soviet researchers as a treatment for exposure to radiation; this aspect of its action is discussed and expanded upon in the commentary under Melatonin. It is also known by the trade name Mexamine and has been looked at as a potentiator of centrally active drugs. Here, as with the simpler N,N-dialkyltryptamines, the metabolic introduction of a hydroxyl group at the 6-position (to give 6-HO-5-MeO-T) leads to a lowering of pharmacological potency. And again, no human studies have been reported.

A true academic challenge exists with the many studies of 5-methoxy-DMT (as has been mentioned under DMT, different drug, same problem) which have involved drug mixtures. The second drug, added to the tryptamine, is almost always a monoamineoxidase inhibitor such as harmaline, either as a chemical (in most clinical studies in the Northern Hemisphere) or as the plant decoction (in most jungle uses in the Southern Hemisphere). The challenge is, just how should one classify these observations? Under the first drug modifying or being modified by the second? Under the second drug modifying or being modified by the first? Or should the mixture be treated as a variable thing in its own right?

Since the mixture invariably shows properties that neither component can show alone, it is obvious that the combination is a major classification component. When the harmaline component is a plant mixture containing harmaline, a common name that is used is Ayahuasca. This can be any of a large number of carboline-containing plants (or even harmaline itself) combined with a really wide variety of amines, ranging from the tryptamines to mushrooms, to such diverse materials as Jimpson Weed components. These combinations are usually unknown as to exact composition, and they will be discussed in a chapter devoted to just this combination, entitled "Hoasca vs. Ayahuasca." On the other hand, when the components are discrete compounds, the process is much more controlled (in the experimental sense rather than in the effects sense) and these combinations are gathered in the recipe for harmaline.

There are a couple more entries for 5-MeO-DMT, one very important, and the other quite trivial. There is a drug-use phenomenon that is often referred to by the popular title of "toad-licking." The toad involved is the Sonora Desert Toad, also called the Colorado River Toad, and carries the binomial *Bufo alverius*. It is not the closely related marine toad *Bufo marinus,* as some people have insisted, prompted by the early Olmec and Mayan iconography. Of course the licking myth is newspaper hype — it is the venom that is active, and it is smoked. When the desert toad is stroked near the parotid glands in the neck region, there is the squirting out of this venom and when it is allowed to dry on a hard surface it takes on the texture of rubber cement. It contains up to 15% 5-MeO-DMT, as well as N-methyl-5-methoxytryptamine, 5-MeO-NMT and Bufotenine, which have their own entries.

And here is the trivial entry. I involved myself in a small Australia/toad incident when I recently visited Sydney. There is a consistent historical record of the axiom "the road to Hell is paved with good intentions" in the effort to import solutions to problems that were the unforeseen consequences of earlier imported solutions. I can't recall the decade-by-decade record but, as I remember, it involved, amongst other things, dogs, rabbits, viruses to control rabbits, and maybe mongooses. And cattle. Cattle had been imported mid-century as a desired agricultural commodity, but it could not be predicted that their cow-plops would not deteriorate. There were domestic dung beetles, but they appreciated kangaroo droppings (raisin-sized) rather than cow-plops (birthday-cake sized). So the eggs of a cow-oriented dung beetle were brought in about 1970 and, after weathering the usual quarantine, were released into the ecosphere. Another beetle came in without invitation with the importation of agricultural cane. Hitch-hiking along with the cane was a cane

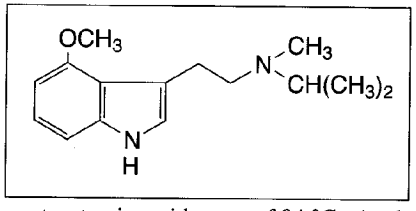
beetle, and it had no natural enemies. The beetle proliferated, and as a solution to this infestation there was brought in a "cane toad," the *Bufo marinus* (the marine toad, not the desert toad, to the eventual disappointment of the drug-oriented subculture) which was believed could provide some control over them. Well, it turned out that the beetles lived at the top of the cane stalks, and the frogs lived at the bottom. The toads didn't eat the beetles, but they did successfully reproduce and multiply because they, too, had no natural enemies. They are today sweeping across north-eastern Australia.

In the middle of downtown Sydney, right alongside Hyde Park at Williams and College, there is the Australian Museum, with a superb library of natural history which I wished to use in the pursuit of the Aborigine use of red beans. And there was a special exhibit on display of the frogs and toads of Australia, with histories, photographs, and occasional soundtracks of croakings. I spotted a panel devoted to the origins and short history of the *Bufo marinus*. And right in front of it was a little old lady diligently reading the text which said, approximately, that a virus was being developed at some research laboratory in South America that would be specific for this toad, and which would bring the problem under control. I wondered to myself, but just loud enough for her to hear, if this was the same virus that could cause the AIDS syndrome in the Wallaby?

She looked at me for a moment, turned, and walked away. Maybe, just maybe, another rumor of unknown origin has been launched.

#39. 4-MeO-MIPT; TRYPTAMINE, N-ISOPROPYL-4-METHOXY-N-METHYL; INDOLE, 3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]-4-METHOXY; N-ISOPROPYL-4-METHOXY-N-METHYLTRYPTAMINE; 3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]-4-METHOXYINDOLE

SYNTHESIS: A solution of 4.0 g of 4-methoxytryptamine in 50 mL toluene was combined with another containing 5.52 g K_2CO_3 in 50 mL H_2O and vigorously stirred at room temperature. To this there was added, dropwise, a solution of 3.0 mL benzyl chloroformate in 20 mL toluene. Stirring was continued for 15 h, then the reaction was treated with 200 mL EtOAc, the organic layer separated, and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum, and the solid residue recrystallized from Et_2O/hexane to give 3.9 g N-(benzyloxycarbonyl)-4-methoxytryptamine with a mp of 84 °C. Anal: $C_{19}H_{20}N_2O_3$. C,H,N.



A suspension of 0.76 g LAH in 50 mL THF was stirred under an inert atmosphere, and treated with the dropwise addition of a solution of 2.5 g

N-(benzyloxycarbonyl)-4-methoxytryptamine in 30 mL anhydrous THF. The reaction mixture was held at reflux for 30 min, then cooled to 40 °C and the excess hydride destroyed with the addition of 50% aqueous THF. The solids were removed by filtration, washed with THF, the filtrate and washings combined, and the solvent removed under vacuum. The residue, impure 4-methoxy-N-methyltryptamine, was dissolved in 50 mL EtOH, treated with 1.0 mL acetone, then with 0.5 g 10% Pd/C, and the reaction mixture shaken under a H_2 atmosphere at 50 psi for 15 h. The catalyst was removed by filtration through a bed of Celite, the filtrate stripped of solvent under vacuum, and the solid residue recrystallized from Et_2O/hexane to give 0.51 g N-isopropyl-4-methoxy-N-methyltryptamine (4-MeO-MIPT) which had a mp 80-81 °C. Anal: $C_{15}H_{22}N_2O$. C,H,N. MS (in m/z): $C_5H_{12}N^+$ 86 (100%); indolemethylene$^+$ 160 (4%); parent ion 246 (6 %).

DOSAGE: 20 - 30 mg, orally

DURATION: 4 - 6 h

QUALITATIVE COMMENTS: (with 10 mg, orally) "In 30-40 minutes, I found I could get some distortions of objects around me, if I really tried hard. There are no color changes. It is unexpectedly mild, and I have no anxiety, no tachycardia. At the two hour point, the peak must be past, and I feel somehow disappointed. I am not sure, in retrospect, if there was ever anything there at all."

(with 17 mg, orally) "I am aware of this at 40 minutes, and was in a very light but not very well defined place for about two hours. It was neither good nor bad. It kind of drifted away and I was not sure when I regained baseline."

(with 26 mg, orally) "I took this orally, in dilute hydrochloric acid so that it would be in solution going down. I was aware in 20 minutes, and went right up to a +3 within the hour. That was quite a bit of change in a half hour. Extremely erotic, but absolutely no visuals to music, either with eyes open or with them closed. I know I am at +3 since there is no way I could drive a car, not for anything in the world, but why not? Don't know, but no way. Cold gaspacho tastes superb, but one cup is enough, and the croissant seems dry and hard. By seven hours I am back where I started from again. Pity."

(with 26 mg, orally) "This is my first try with this drug, ever. First indications of effects in twenty minutes. Quiet onset, no remarkable visuals, in fact no particular visuals at all. To a + 2 within about ten or fifteen minutes more. Body is comfortable, mind-set pretty much unchanged from baseline. No euphoria, no insights. But also, no discomfort. Erotic was extremely successful, and orgasm seemed easier than with other materials. Still no visuals but seemed to be a soft +3. Music fine. Hard to define exactly how we knew we were in an altered state, because of the lack of visual clues. Body aware more than mind. Would like to explore this further. Perhaps for writing? Nice material. Maybe higher next time?"

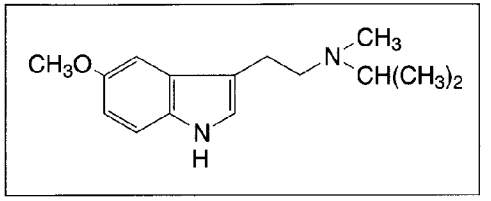
EXTENSIONS AND COMMENTARY: It seems to me to be somehow a pivotal compound, in that it carries the pattern of nitrogen substituents that appears to be the most effective orally (the methyl group and the isopropyl group) and it is oxygenated in the aromatic ring. Both the 4-hydroxy analogue (4-HO-MIPT) and the 5-methoxy analogue (5-MeO-MIPT) are very active at these levels. Perhaps if the oxygen is in the 4-position it must be exposed as in psilocin to reveal an active zwitterion. And if the oxygen is in the 5-position, it must be masked as a methyl ether to hide its intrinsic polarity. But these are observations, not explanations. Why is this compound, 4-MeO-MIPT, so seductive and appealing a hybrid, not as potent as one might expect? The remaining two, the 6-isomer and the 7-isomer, are described in the recipe for 5-MeO-MIPT.

A similar discussion could be made about the corresponding compounds that possess the N,N-dimethyl pattern of DMT. Again, there are a total of four possible ring-methoxylated isomers. The 5-substituted compound is 5-MeO-DMT and, as it is remarkably potent, it is given its own entry. However, the other three monomethoxy analogues, 4-methoxy-, 6-methoxy- and 7-methoxy-N,N-dimethyltryptamine, remain relatively unknown.

The 4-methyl ether of psilocin, 4-MeO-DMT, is especially appealing, in that it is a simple homologue of psilocin and it is quite stable. But the methyl group as an ether link lacks the lability of the phosphate or acetate esters, and it cannot be easily hydrolyzed off to form psilocin. The immediate homologue is 4-MeO-DET, which is completely without action either orally or by smoking at dosages up to 30 mgs. The two remaining DMT isomers are with the methoxy at the 6-position (to give 6-MeO-DMT, originally thought to be a minor alkaloid in *B. caapi*) and at the 7-position (to give 7-MeO-DMT, which was observed as a minor impurity in the preparation of 7-MeO-MIPT). Some rat studies were performed in the mid 60's on all three of these compounds. A couple of years later the 4-isomer was studied in the squirrel monkey and found to have weak central activity (size discrimination studies with rewards of grapes, underwater maze running with rewards of simply being allowed to survive). These studies suggested that it was not very potent, certainly much less potent than 5-MeO-DMT, but no trial has as yet been reported in man for any of these three isomers. If this lower potency were to hold up in human trials, it would give additional support to the positional parallels between the "4-position" of the phenethylamines, and the "5-position" of the tryptamines. That is where, indeed, the action is to be found. All of these methoxylated DMT analogues will probably be pretty easily destroyed metabolically, so some parenteral route might have to be used in exploring them. Right here, in the above preparation, 4-methoxy-N-methyltryptamine (4-MeO-NMT) has been made as a chemical intermediate, but it was not characterized, and no spotlight was put on it as a potential drug in its own rights. It is the ether that corresponds to the natural ester baeocystin, and it probably wouldn't come off gracefully, either chemically or metabolically. There is yet another mushroom analogue here. The starting material is the bare tryptamine itself, 4-MeO-T, which is the ether counterpart to norbaeocystin.

#40. 5-MeO-MIPT; TRYPTAMINE, N-ISOPROPYL-5-METHOXY-N-METHYL; INDOLE, 3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]-5-METHOXY; N-ISOPROPYL-5-METHOXY-N-METHYLTRYPTAMINE; 3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]-5-METHOXYINDOLE

SYNTHESIS: To a solution of 1.40 g 5-methoxy-N-methyltryptamine (5-MeO-NMT, see separate recipe) in 50 mL methanol there was added 1.0 mL acetone and 0.5 g 10% Pd/C. This mixture was shaken under a H_2 atmosphere at 50 psi for 15 h. The catalyst was removed by filtration through a bed of Celite, the filtrate stripped of solvent under vacuum, and the solid residue recrystallized from Et_2O/hexane to give 1.45 g N-isopropyl-5-methoxy-N-methyltryptamine (5-MeO-MIPT). This was isolated as the hydrochloride salt by dissolving it in a small amount of IPA, neutralization with concentrated HCl, and dilution with Et_2O. This had a mp 162-163 °C. Anal: $C_{15}H_{23}ClN_2O$. C,H,N. MS (in m/z): $C_5H_{12}N^+$ 86 (100%); indolemethylene$^+$ 160 (5%); parent ion 246 (4%).



DOSAGE: 4 - 6 mg, orally;
12 - 20 mg, smoked

DURATION: 4 - 6 h

QUALITATIVE COMMENTS: (with 1.5 mg, orally) "In 15 minutes I was already off baseline, and by an hour it is unquestionably real. There is no visualization to music, but a general turned-on randiness. Dropping at an hour and a half, and out by three hours. Modest but real."

(with 4 mg, orally) "Up very fast, to a +2 in an hour. Absolutely no visuals, but over the next two hours an ease of interpretive fantasy, almost dream-like, and easy eroticism. Food tasted marvelous, but there was no appetite. Easy, normal sleep and good spirits in the AM."

(with 5 mg, orally) "Extremely bitter taste. Some stimulation and tingling at 10 minutes, and I am apprehensive at this rapid onset. There are no visual symptoms at all, but the stimulation of conceptual thought is intense. Depth perception is slightly altered and a very minor wave pattern can be noticed in the peripheral vision, but no major object or color distortion. Minor enhancement of auditory acuity. Philosophical concepts about this and other substances seem important. I wonder what the value of writing about, or attempting to describe, their effects really is. At the second hour, the effects are subsiding, and for another three hours there are tailings and insomnia, but I am able to eat normally. There is a certain

amount of 'negativity' about this compound. The dose is satisfyingly small, but I wonder if it is worth it. Somewhat of a disappointment. Have no desire to experiment further."

(with 6 mg, orally) "Rapid development to 45 minutes, some shakes, uneven handwriting, and hints of time slowing. Extremely erotic. Full plateau at a +3 at the 2 1/2 hr. point, then a graceful and rather rapid drop. Easy, restful sleep. Absolutely no visuals or related sensory effects — what does one call this stoned state? Very pleasant, music extremely acceptable, tactile extraordinary. I feel that higher dosages would not contribute anything more."

(with 12 mg, smoked) "I was able to take 4 or 5 puffs, and to hold off the onset until then, then I couldn't anymore. Powerful, tremendous rush, but all along maintaining body-ego awareness, unlike 5-MeO-DMT where the world appears to utterly dissolve. I was aware of doing a lot of groaning, writhing, shaking around; headphones and eyeshades kept it completely internal. Not too much visual, but lots of disorientation. Early on there was a lot of emotional lability, laughing, crying, 'Oh God' kinds of outbursts.

"At an hour and a half, I was down enough that I tried smoking the remainder of the bowl without much additional effect. A typical psychedelic afterglow and in the morning ate a big breakfast and felt essentially normal. In summary, I took too little, I was in a bad mood, and felt myself to be in a rushed environment. The experience seemed to me like a hybrid between CZ-74 and 5-MeO-DMT; the trippiness of the former and the rush (although not as intense) of the latter."

(with 20 mg, smoked) "Most all of it was smoked in about three or four inhalations before I felt it coming on so strongly that I lay down. Within less than a minute after I lay down, with my eyes closed, my visual field was filled with brilliant geometric, patterned lines of different colors that were slowly moving. There were several sets of parallel and curved lines superimposed upon each other. Soon after that, probably within a minute or two, I became extremely disoriented from my normal sense of being a person in a body; I was lost in an undifferentiated mass of feeling and non-specific sensation. It was similar to the overwhelming feeling of 5-MeO-DMT in quality and, as with that material, the peak phase lasted less than 30 minutes.

"Then I began to think more coherently, but intense waves would return every 5 to 15 minutes. In between, my perception and thinking would be fairly normal, but with the waves I would be swept up in imagery or memories heavily laden with emotional content. After two hours I was joined by my wife. We spent some very intimate time together, and I remember asking her who she was and she replied, 'Your wife.' This was very powerful to me since I did not really know what it meant, except that it seemed to be the best combination of mother, lover and friend, and that it was an entirely new kind of relationship that we would be creating for the rest of our lives together.

"After three or four hours, the waves had virtually stopped, and I remained oriented to the present and my immediate surroundings. I stayed under a mild influence until I ate supper, around 7 hours. I felt tired, had trouble falling asleep, but awoke refreshed."

EXTENSIONS AND COMMENTARY: In my lecturing at the University, every couple of years or so some student uses the term "more unique than" or "relatively unique." This immediately triggers a reflex response from me, to emphasize the simple definition that something that is unique is something that is one of a kind, and that all one-of-a-kind things are different from all other one-of-a-kind things. All drugs are unique. Every drug is different from all other drugs. 5-MeO-MIPT is unique.

The last two entries in the "Qualitative Comments" section are longer than usual, but even at that they have been trimmed down from reports sent to me that were each over three pages in length. A thread common to each of them is the comparison of the effects of smoking 5-MeO-MIPT to those from smoking 5-MeO-DMT. The speed of onset, the intense depersonalization and loss of immediate contact with one's surroundings, the impressive recall of early memories and the significance of these memories, make the drugs appear similar to one another. And the fact that they are of similar potency when smoked (5-MeO-DMT is perhaps a tad more potent) makes the relationship more comfortable. And then, with the eye of a chemist making further comparisons, the whole structure-activity relationship falls into place. The formulae are identical, except that one of the N-methyl groups of 5-MeO-DMT is extended by a couple of carbon atoms, to an isopropyl group in 5-MeO-MIPT. They are almost the same. They have almost the same action when smoked. They are "unique and similar" and together they appear to be quite different from the rest of the pack. Nope, that is just not so! They are totally different from one another.

All you need to do, to see that clearly, is to look at that one additional observation involving oral activity. This drug, 5-MeO-MIPT, is several times more potent when taken orally than it is when smoked. 5-MeO-DMT is much less active orally than when it is smoked. As a matter of fact, it is not active at all when taken orally. No active oral level has ever been found. What a rich area for speculation. Preferential metabolism? First pass goings-on? Chemical change from pyrolysis in the pipe? Different receptors? Lipophilicity? I am reminded of the quote from Mark Twain: "I like science because it gives one such a wholesome return of conjecture from such a trifling investment of fact."

Might the observations of the remaining oxygen-substituted MIPT's provide additional clues? There are four possible mono-methoxylated MIPT's; all have been synthesized and all have been explored in man. The 4-methoxy-isomer was of modest activity and deserves, and has received, a recipe of its own. The 5-methoxy-isomer is the one described here, and is extremely potent (orally, but less so parenterally). But as one goes to the 6- and 7-positional isomers, the two remaining positions, the psychopharmacological activity seems to be lost. This is

a humorous reminder of the British idiom, to be at 6-'s and 7-'s about something.

6-MeO-MIPT was made from the corresponding indole, by reaction with 2-nitroethyl acetate, the resulting 3-nitroethylindole catalytically hydrogenated to 6-MeO-T, which was converted to the N-benzyloxycarbonyl derivative. This was reduced to 6-MeO-NMT, which was in turn reductively coupled with acetone to provide 6-MeO-MIPT, with a mp of 89-91 °C and an overall yield of 9%. MS (in m/z): $C_5H_{12}N^+$ 86 (100%); indolemethylene$^+$ 160 (7%); parent ion 246 (4%). In human trials there was one report of some kind of neurological twinge at a 16 milligram level, but nothing else at trials of up to 50 milligrams and it has been shelved as being inactive.

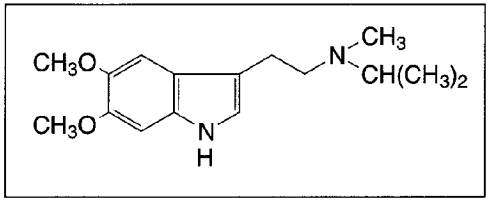
The isomeric 7-MeO-MIPT was synthesized by the exact same five-step reaction sequence starting with 7-methoxyindole, in an overall yield of 24%. The actual reaction conditions for this conversion are detailed in the recipe for 4-MeO-MIPT. The mp of 7-MeO-MIPT was 72-73 °C and its MS (in m/z): $C_5H_{12}N^+$ 86 (100%); indolemethylene$^+$ 160 (5%); parent ion 246 (4%). Gas chromatographic analysis indicated that the product was only 80% pure, and three of the impurities were identified. One was 7-MeO-NIPT with MS (in m/z): $C_4H_{10}N^+$ 72 (100%); indolemethylene$^+$ 161/160 (13, 8%); parent ion 232 (4%). Another was 7-MeO-DMT with MS (in m/z): $C_3H_8N^+$ 58 (100%); indolemethylene$^+$ 160 (6%); parent ion 218 (9%). The third was 7-MeO-NMT with MS (in m/z): $C_2H_6N^+$ 44 (100%); indolemethylene$^+$ 161/160 (82, 39%); parent ion 204 (5%). These three impurities represented approximately 5%, 3%, and 4%, resp., of the isolated product's final weight. It showed something going on at 20 mg orally with perhaps a little distortion in the visual field. And, separately, at 70 milligrams orally there might have been a light-headedness after a few minutes. Nothing more. It, too, has been given the kiss of death by being declared inactive at the 50 milligram level.

The last of the Mohicans, the tribe of compounds with the remarkably potent, orally active, N-methyl-N-isopropyl system on the tryptamine nitrogen atom, was the dimethoxy analogue with both the 5- and the 6-positions occupied with methoxy groups. This specific compound has its own recipe as it raises specific questions that deserve direct attention. The very close relative with the methylenedioxy group at this 5,6-location also has a separate recipe.

Two final laments. Remember that all these beautiful compounds are unique. Why do they behave the way they behave? I have no idea, and there never are enough data to explain everything. I hate the fact that the word data is plural. But singular or plural keep collecting it (them), and keep trying to make sense of everything. And, a small point from my infancy. *The Last of the Mohicans* was one of the very first books I read, and I had very innocently accepted the footwear of these Indians as being the metaphor for the people themselves. I had seen that title as, "The Last of the Moccasins." This is a pair of words that I still interchange without any defense, along with shoulder and soldier, avatar and atavar, and especially annoying when lecturing, irrelevant and irreverent.

#41. 5,6-MeO-MIPT; TRYPTAMINE, 5,6-DIMETHOXY-N-ISOPROPYL-N-METHYL; INDOLE, 5,6-DIMETHOXY-3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]; 5,6-DIMETHOXY-N-ISOPROPYL-N-METHYLTRYPTAMINE; 5,6-DIMETHOXY-3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]INDOLE

SYNTHESIS: To a suspension of 0.88 g 5,6-dimethoxyindole in 50 mL Et_2O, stirred and cooled with an external ice bath, there was added, dropwise, a solution of 0.87 g oxalyl chloride in 5 mL Et_2O over the course of 20 min. The mixture was stirred for an additional 20 min, and then the glyoxyl chloride was removed by filtration, washed with Et_2O, and dried under vacuum. A suspension of this red solid in 50 mL of ice-cold dry THF, under nitrogen, was treated with the dropwise addition of a 30% solution of methyl isopropyl amine in Et_2O, until the pH exceeded 9. The solvents were removed under vacuum, and the residue partitioned between $CHCl_3$ and H_2O. The organic phase, after decolorization with charcoal, was stripped of solvent under vacuum and the solid residue recrystallized from EtOAc/hexane. There was thus obtained 0.61 g 5,6-dimethoxy-N-isopropyl-N-methylindoleglyoxylamide, with mp 204-206 °C (yield 40%).



A well-stirred suspension of 0.55 g LAH in 25 mL anhydrous THF was treated, dropwise, with a solution of 0.53 g 5,6-dimethoxy-N-isopropyl-N-methylindoleglyoxylamide in 75 mL anhydrous THF. The reaction mixture was brought to reflux temperature, held there for 30 min, and cooled to about 40 °C. There was added 0.55 mL H_2O followed by 1.65 mL 10% aqueous NaOH and an additional 0.55 mL H_2O. The solids were removed by filtration and the filter cake washed with THF. The combined filtrate and washings were stripped of solvent under vacuum. The oily residue was crystallized from hexane to give 0.34 g (yield 71%) 5,6-dimethoxy-N-isopropyl-N-methyltryptamine, mp 71-73 °C. MS (in m/z): $C_5H_{12}N^+$ 86 (100%); indolemethylene$^+$ 190 (4%); parent ion 276 (9%).

DOSAGE: > 75 mg, orally

DURATION: unknown

QUALITATIVE COMMENTS: (with 35 mg, orally) "Nothing at all."

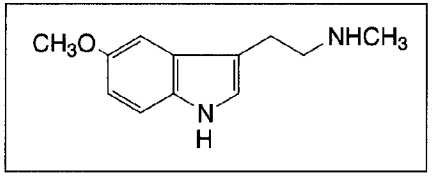
(with 75 mg, orally) "There was a vague awareness of something at about the one-hour point. Not enough to even be called a threshold effect."

EXTENSIONS AND COMMENTARY: This compound, having no detectable activity even at the milligram/kilo level, pretty much condemns the 5,6-dimethoxy indole pattern. Quite a few closely related derivatives have been made; there is the N,N-dimethyl (5,6-MeO-DMT), the N,N-diethyl (5,6-MeO-DET), the N,N-dibutyl (5,6-MeO-DBT) and the three famous heterocyclic ring compounds, the pyrrolidyl (5,6-MeO-pyr-T), the piperidyl (5,6-MeO-pip-T) and the morpholyl (5,6-MeO-mor-T) compounds. They were all synthesized and characterized in the 1960's, but I have no record of any having been tried in man.

One desoxy analogue warrants mention. This is known as 5-methoxy-6-methyl-DMT (5,6-MeOM-DMT) or as 5-methoxy-6,N,N-trimethyltryptamine (5-MeO-6,N,N-TMT), where the 6-methoxy group is, in effect, replaced with a 6-methyl group. Having a DMT skeleton, it was assayed parenterally, and even at 15 milligrams (smoking) there was nothing noted. This is a level that would have been dramatic had there been no substitution at that 6-position. Some of the historical background of an oxygen at this position is discussed in the 6-HO-DMT recipe.

#42. 5-MeO-NMT; N,O-DMS; NOR-5-MeO-DMT; TRYPTAMINE, 5-METHOXY-N-METHYL; INDOLE, 5-METHOXY-3-[2-(METHYLAMINO)ETHYL]; SEROTONIN, N,O-DIMETHYL; 5-METHOXY-N-METHYLTRYPTAMINE; 5-METHOXY-3-[2-(METHYLAMINO)-ETHYL]INDOLE; N,O-DIMETHYLSEROTONIN

SYNTHESIS: (from 5-MeO-DMT). To a solution of 0.10 g 5-methoxy-N,N-dimethyltryptamine (see 5-MeO-DMT) in 5 mL benzene there was added 0.5 g 2,2,2-trichloroethyl chloroformate, and the resulting solution was held at reflux temperature for 2 days. After cooling there was added 5 mL Et_2O and the organic phase washed with 2x20 mL 3N HCl followed by 20 mL H_2O. The solvent was then removed under vacuum. The residue (N-(2,2,2-trichloroethoxycarbonyl)-N-methyl-5-methoxytryptamine, 0.12 g) was dissolved in 2 mL acetic acid and treated with 0.15 g powdered zinc. After stirring for 4 h at room temperature, the reaction mixture was filtered and the filtrate made basic with 3N NaOH. This was extracted with 3x20 mL Et_2O, the extracts pooled, and the solvent removed under vacuum. The residue was purified by preparative TLC, using a BuOH/AcOH/H_2O (12/3/5) solvent for development. There was thus obtained 0.013 g of 5-methoxy-N-methyltryptamine (5-MeO-NMT) as a solid with a mp of 90-93 °C.



(from 5-MeO-T) A solution of 0.086 g 5-methoxytryptamine (5-MeO-T) in 1 mL dioxane containing 0.5 mL of 2N NaOH was cooled to 0 °C and well-stirred. There was added, at the same time, 0.2 mL benzyl chloroformate and 0.25 mL 4N NaOH. This was allowed to come to room temperature and the stirring was continued for an additional 10 min. There was added concentrated HCl, followed by 10 mL H_2O. This mixture was extracted with 3x20 mL Et_2O, the extracts pooled, and the solvent removed under vacuum. The crude carbamate was purified by silica-gel column chromatography using n-hexane/CH_2Cl_2 (1/9) as an eluting solvent. After removal of the chromatographic solvent under vacuum, the residue was dissolved in 10 mL anhydrous THF and added slowly to an ice-cold, well-stirred suspension of 0.178 g LAH in 10 mL anhydrous THF. After being brought to reflux and held there for 4 h, the mixture was cooled and acidified with 1N HCl. The THF was removed under vacuum, and the aqueous residue washed with Et_2O. This was then treated with solid $NaHCO_3$ and extracted with 3x50 mL Et_2O. The solvent from the combined extract was removed under vacuum, and the residue purified by preparative TLC as described above. There was thus obtained 0.016 g of 5-MeO-NMT with a mp of 88-91 °C.

DOSAGE: (not known)

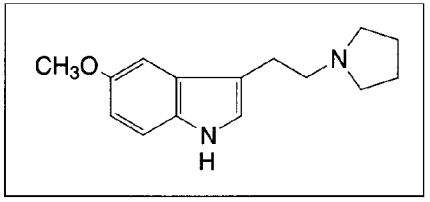
DURATION: (not known)

EXTENSIONS AND COMMENTARY: This base is the botanically and pharmacologically famous 5-MeO-DMT, missing one of its two N-methyl groups. Sort of a nor-5-MeO-DMT. Its human exploration has just been started, but the expected vulnerability of it to metabolic oxidative deamination makes it a good guess that it (as seen with the dimethyl homologue) will only be active parenterally, or when the body's destructive enzymes are held at bay by effective monoamine oxidase inhibition. This base has been found in several *Virola* species but, as it is always accompanied by 5-MeO-DMT, its contribution to the psychoactivity of the resulting snuff is completely unknown. It has also been found in the skin of the *Bufo alvarius* at the trivial level of 20-23 micrograms per gram, compared to skin levels of 1.0 to 3.5 mg/g of 5-MeO-DMT.

A fascinating cyclization product of this "nor-compound" is a cyclic dehydrogenation product where there is a direct coupling of the tryptamine nitrogen to the 4-position of the indole ring. This tricyclic material, O-methyl-nordehydrobufotenine, proved to be of comparable activity to DMT in rat studies, but has not apparently been studied in man.

#43. 5-MeO-pyr-T; TRYPTAMINE, 5-METHOXY-N,N-TETRAMETHYLENE; INDOLE, 5-METHOXY-3-[2-(1-PYRROLIDYL)-ETHYL]; PYRROLIDINE, 1-[2-(5-METHOXY-1H-INDOL-3-YL)ETHYL]; 5-METHOXY-N,N-TETRAMETHYLENETRYPTAMINE; 5-METHOXY-3-[2-(1-PYRROLIDYL)ETHYL]INDOLE; 1-[2-(5-METHOXY-1H-INDOL-3-YL)ETHYL]PYRROLIDINE; "PYRROLIDYL-5-METHOXY-TRYPTAMINE"

SYNTHESIS: To a well-stirred solution of 1.25 g 5-methoxyindole in 15 mL TBME there was added, dropwise, a solution of 1.1 g oxalyl chloride in 15 mL TBME, over the course of 20 min. Stirring was continued for an additional 10 min during which time there was the separation of 5-methoxyindol-3-ylglyoxyl chloride as a tomato-red crystal, which was removed by filtration and washed with a small amount of TBME. The loose crystals were added, a bit at a time, to 2.0 mL well-stirred pyrrolidine, and the stirring continued until the red color had dissipated and the solids had returned to room temperature as a cream-colored paste. There was then added 80 mL of 1 N HCl which produced a product with a loose crystalline texture. This was removed by filtration, yielding, after air drying at 100 °C to constant weight, 1.13 g of a cream colored material with a mp in the 180-195 °C area. Recrystallization from 15 mL of boiling MeOH gave, after cooling and filtering, 5-methoxyindol-3-yl-N,N-tetramethyleneglyoxylamide as a white crystalline solid weighing, after air-drying to constant weight, 0.65 g (28%) with a mp of 211-212 °C. IR (in cm^{-1}): 700, 741, 792, 1013, 1150, 1188, with a broad carbonyl centered at about 1620 and the indolic NH stretch a broad peak at 3160.



A solution of 0.52 g 5-methoxyindol-3-yl-N,N-tetramethyleneglyoxylamide in 15 mL anhydrous dioxane was added, slowly, to 0.80 g LAH in 15 mL dioxane, which was well-stirred and held at reflux temperature under an inert atmosphere. After the addition was complete, reflux was maintained for an additional 16 h, the reaction mixture cooled, and the excess hydride destroyed by the cautious addition of wet dioxane. The formed solids were removed by filtration, washed with hot dioxane, the filtrate and washings combined, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum. The pale amber residue was distilled at the KugelRohr at 160-170 °C at 0.05 mm/Hg to give 0.11 g (23%) of 5-methoxy-N,N-tetramethylenetryptamine as an off-white oil that did not crystallize. MS (in m/z): $C_5H_{10}N^+$ 84 (100%); indolemethylene$^+$ 160 (4%); parent ion 244 (6%). The hydrochloride salt was prepared by treating an Et_2O solution of the free base with anhydrous hydrogen chloride gas, and recrystallizing the formed solids from MeOH/benzene. The mp was 164-167 °C.

DOSAGE: 0.5 - 2 mg, orally; 2 -3 mg, smoked

DURATION: several hours

QUALITATIVE COMMENTS: (with 0.5 mg, orally) "This stuff is an absolute poison. Within minutes I noticed what can only be called ear-ringing without any ear-ringing. Intense tinnitus with no sound, most uncomfortable. There were two waves of nausea and vomiting of yellow bilious stuff, with thick mucus for saliva. I can't think straight — muddled. I can't get answers to questions because I simply cannot form the questions. Eyes closed to music gave no images, but the music sounded OK. Recovery was quite rapid, and I was together again in a few hours. Never again."

(about 1 mg, smoked) "I managed to vaporize about a milligram of the material, and there was nothing profound. There was a slight feeling of calmness. As I felt sure that this material would be a quieting agent, I managed to vaporize and inhale what might have been up to another milligram. There were no psychedelic effects manifested, and I fell asleep easily 10 minutes later."

(with 3 mg, smoked) "Initially the compound exhibited a 5-MeO-DMT-like effect. There was a total loss of self-identity in a nearly instantaneous rush. I felt as if the top of my head was blown off at the onset of the drug experience. My observers told me that I had been unconscious for four hours. I remember reentering with the feeling 'God is Love.' After completely coming to, I felt very nauseous, and threw up in the bathroom several times. I felt drained and sick for the rest of the evening as well as mentally slow. By the next morning I was more alert and responsive. I have absolutely no memory of anything that transpired while I was on the compound."

(with 3 mg, smoked) "I inhaled the vaporized sample at 10 past noon. There was quite a rush. There were none of the shifting shapes, colors and forms of DMT. Nor was it acute with clarity or energy as with my many experiences with 5-MeO-DMT. The effect was intense but not terrifying, with a full body buzz and with humming resonance as I fell backwards into something where all memory was lost. I was told that at 18 past noon, I was unconscious. Something over an hour later, I started flailing, rolling about, quivering and shaking, and had very constricted pupils. In another hour I was able to talk lucidly, but quietly. In yet another hour, I was nauseous and tried for the bathroom, but didn't make it. The people who were watching me were alarmed. My actions were scary. And my skin looked funny for several days afterwards. There are long-lasting properties of this. My first exposure was with perhaps a milligram (smoked, also) and the effects were substantial, with rough edges and minor dysphoria."

(with 4 mg, smoked) "This was the free base. I remember the pipe, and the inhalation and, with the pouring of a small glass of scotch, I settled down in front of the TV to watch a re-run of Star Trek. That was it. I came to some time later in

the front room of a professional ally of mine, who had by chance discovered me walking down the street near his house. I do not recall, nor have I been able to regain, any memories of the time I was 'out there.' I apparently experienced no physical discomfort from the drug. In fact I distinctly remember feeling very comfortable when I awoke. Clearly this compound is some weird-ass shit."

EXTENSIONS AND COMMENTARY: Again, as with other compounds in these writings, there is an irresistible urge to present generalizations. But with this particular material, there are obvious unresolved problems with both dosage or duration, and I am limited to the few comments provided above. Dosage? A very few milligrams parenterally, but with smoking such small amounts it is hard to accurately estimate the actual dosages received. Duration? One subject could be fine the next morning, and another could be still aware of wrongness a week later. I am uncomfortable with any compound that seems to be widely variable in its impact on different people.

The qualitative aspects of these (and other) reports imply some individual variability. It is always easy to look at tryptamines such as this one, or the others in these recipes, and say, "We know that they are psychedelics. And maybe good ones or maybe bad ones. So we should look at them with that preconceived notion in mind." But looking objectively at this particular compound, 5-MeO-pyr-T, we are far away from any vocabulary of psychedelics. How is it different from, say, what one might expect from a Fentanyl analogue? Here is a collection of trials that describe parenteral administration and the quick development of an anesthesia. This compound may not be the new Fentanyl because of the nausea during what would be the recovery period. But what are the chances that, perhaps not with this compound, but with any of the obvious analogues that are screaming to be assayed, there just might be a useful clinical tool?

There is another message of warning. Here one must accept the eloquent argument that, for the structuring of an experiment with an unknown and thus undefined new drug, there must be observers present who are both sober and sympathetic. The heroic and macho "I'll do it my way" can lead to both psychological problems and physical risks. As with scuba diving, always work with a partner.

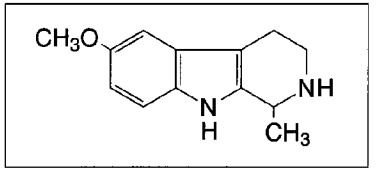
With both pyr-T and 4-HO-pyr-T, there are two additional ring analogies that are natural companions to 5-MeO-pyr-T. These are the piperidine and the morpholine counterparts, 5-MeO-mor-T and 5-MeO-pip-T. Both compounds are in the literature, and an entry reference to them can be gotten from the "known tryptamines" appendix. Along with the pyrrolidine material I had made a reasonable supply of the amides for these other two, both by way of the 5-methoxyindole and oxalyl chloride procedure given above. With piperidine, there is 5-methoxyindol-3-yl-N,N-pentamethyleneglyoxylamide, mp 167-169 °C and IR, (in cm^{-1}), 730, 780, 811, 928, 1033, 1161, a broad carbonyl at 1600 and a broad indolic NH stretch at 3190. With morpholine, the corresponding glyoxylamide melted at 193-194 °C,

with an IR spectrum (in cm^{-1}), of 747, 791, 856, 925, 976, 1043 and 1122, the carbonyl at 1620 and the broad NH at 3150.

With the rather unexpected, and unencouraging descriptions of the pyrrolidine tryptamines in general, and this one in particular, I was not in too blinding a hurry to explore the two heterocyclic analogues. The amides are still on the shelf in the lab. If some good reason comes forth to assay the final amines, they can be made with a dash of lithium aluminum hydride, but until then I have other things to do.

#44. 6-MeO-THH; HARMAN, 6-METHOXY-1,2,3,4-TETRAHYDRO; β-CARBOLINE, 6-METHOXY-1-METHYL-1,2,3,4-TETRAHYDRO; 6-METHOXY-1,2,3,4-TETRAHYDROHARMAN; 10-METHOXY-3,4,5,6-TETRAHYDROHARMAN; 6-METHOXY-1-METHYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE; 1-METHYLPINOLINE; ADRENOGLOMERULOTROPIN; ALDOSTERONE-STIMULATING HORMONE; MCISAAC'S COMPOUND

SYNTHESIS: (from melatonin): To a gently refluxing solution of 1.6 g melatonin in 120 mL dry xylene there was added in small portions 14 g P_2O_5 over the course of 45 min. The solvent was removed under vacuum, and the residue treated with H_2O, then made basic with dilute NaOH, and extracted with Et_2O. Removal of the solvent from the pooled extracts and recrystallization of the residue from EtOH gave 1 g 6-methoxyharmalan with a mp 205-207 °C. High vacuum sublimation gave a product with a mp 208-209 °C. IR (in cm^{-1}): 801, 824, 849, 990, 1031, 1076, 1182. MS (in m/z): Parent ion -1, parent ion 213, 214 (100%, 83%); 170 (22%); 195 (19%). This base can be dehydrogenated by heating 0.7 g with 3 g of Pd-black in a sealed tube for 30 min at 200 °C. The reaction mixture was treated with hot EtOH, filtered, and the filtrate stripped of solvent under vacuum. This gave 0.4 g 6-methoxyharman with a mp 266-267 °C from aqueous EtOH. The mp after recrystallization from MeOH is reported to be 273-274 °C. IR (in cm^{-1}): 621, 698, 835, 1028, 1075, 1184. MS (in m/z): 197 (100%); parent ion 212 (66%); 169 (37%).



To a solution of 0.10 g 6-methoxyharmalan in 5 mL dilute HCl there was added 10 mg PtO_2 followed by the dropwise addition of 40 mg $NaBH_4$ dissolved in 1 mL of H_2O. The solids were removed by filtration through paper, and the cream-colored filtrate made basic with 5% NaOH and extracted with 4x20 mL portions of CH_2Cl_2. The extracts were pooled, the solvent removed under vacuum, and the solid residue recrystallized from MeOH to give, after air drying to constant

weight, 75 mg of free base 6-methoxytetrahydroharman (6-MeO-THH) as a white solid. IR (in cm^{-1}): 797, 832, 975, 1112, 1121, 1148. MS (in m/z): 201 (100%); 186 (43%); parent ion 216 (38%); 172 (21%); 144 (16%).

(from 5-methoxytryptamine) A solution of 1.00 g 5-methoxytryptamine in 25 mL H_2O was brought to a pH of 4 with 0.1 M HCl and placed under a N_2 atmosphere. There was then added a solution of 1.5 g acetaldehyde in 15 mL of 85% aqueous EtOH. The solution was stirred for 2 days at room temperature, and then made basic and held at 0 °C, allowing crystallization. There was thus obtained 175 mg (19%) of 6-methoxytetrahydroharman (6-MeO-THH) as a white solid, with a mp 160-161 °C. The literature also reports a mp of 224-226 °C.

EXTENSIONS AND COMMENTARY: I have decided to completely eliminate the dosage, duration, and qualitative comments for this compound, and all related harman analogues. The reason is painfully obvious — virtually nothing is known about their psychopharmacology. Despite their enormous potential for someday being understood as possible intermediates in brain chemistry, they remain almost unexplored. I was working closely with Dr. C. Naranjo in the middle '60's in this area, on a study we were considering co-authoring, to be entitled, "Hallucinogenic Properties of a Pineal Metabolite, 6-Methoxytetrahydroharman." This was recorded in the *Ethnopharmacologic Search for Psychoactive Drugs* book of Daniel Efron, as being in Science, in press. But, the paper was never in press, as it had never been submitted for publication, as it had never been written. All of this for the very simple reason that the research for it was never completed. It had just been started. Claudio had explored both 6-methoxytetrahydroharman and the corresponding harmalan in the 100-150 milligram area, and was finding some activity. I was running parallel studies and had gotten up to about 100 milligrams and had not found anything. We both saw this as being a rich and promising virgin field for exploring human pharmacology. It still is rich and promising. And it still is virgin.

Before any particulars, let me offer some rather broad generals about nomenclature. This world of carbolines is a total bear as to the assignment of chemical names, and this is a logical place to talk about it. Many terms will be encountered. Some are totally trivial, such as a specific compound that has been given a name from the binomial of the plant where it had been discovered, as in Leptaflorine from *Leptactinia densiflora*. Some are based on the completely general parent ring system itself, beta-carboline. Many compounds have many synonyms, and the carboline appendix in the back of this book would be a good place to save these names as you find them. For me, I look for middle territory. I look for two clues. The first is a sound that catches my attention immediately, the prefix, "harm-." This demands that there is a methyl group in the molecule and that it is at the 1-position. The second clue is the vowel that follows the harm-. It will usually be an "a" or an "i" or occasionally an "o." The harma- things have nothing on the aromatic ring, and the harmi- things have a 7-methoxy group there, and the harmo-

things are usually phenolic, with an oxygen attachment there. And the numbering systems can be totally off the wall.

Let me try to organize the "harm" chaos first, always with that methyl group at the C-1 position of the carboline ring. The second collection has a hydrogen atom there.

indole sub.	aromatic (H_0)	dihydro (H_2)	tetrahydro (H_4)
	with a 1-methyl substituent		
Ar-H	**harman**	harmalan	**tetrahydroharman** (THH)
Ar-6-OH	6-harmol	6-harmalol	**6-tetrahydroharmol**
Ar-6-OMe	6-MeO-harman	**6-MeO-harmalan**	**6-MeO-tetrahydroharman**
Ar-7-OH	harmol	harminol	**tetrahydroharmol**
Ar-7-OMe	harmine (a)	harmaline (a)	tetrahydroharmine (a)
	with a 1-hydrogen substituent		
Ar-H	βC	DHβC	**THβC (tryptoline)**
Ar-6-OH	6-HO-βC	6-HO-DHβC	**6-HO-THβC**
Ar-6-OMe	6-MeO-βC	6-MeO-DHβC	**6-MeO-THβC (pinoline)**
Ar-7-OH	7-HO-βC	7-HO-DHβC	7-HO-THβC
Ar-7 -OH	7-MeO-βC	7-MeO-DHβC	7-MeO-THβC

(a) has its own recipe
bold, included in this recipe

Some minor stumbling blocks remain in this system. βC (beta-carboline) has been called nor-harman, since it is harman without the methyl group. This is incorrect in theory in that the prefix "nor" implies that the lost group comes from a nitrogen. Incorrect, but common. Many additional synonyms and botanical locations are given in the carboline appendix. And throughout this discussion, I will totally ignore the chemically correct way of naming beta-carboline, which is 9H-pyrid-[3,4-b]-indole.

A brief comment on the numbering systems that can be found. The procedure used here and in the appendix starts counting at the carbon atom of the pyridine ring that is closest to the indole nitrogen. The pyridine nitrogen atom becomes two, and on around, hitting every substitutable atom ending on the indole nitrogen as the 9-position. However, as usually in the older literature but still seen sometimes today, the indole nitrogen is the 1-position (as it still is when a structure is seen as an indole) and then every atom, substitutable or not, is numbered sequentially. This brings the 7-substitution identifier of harmine (which is the

indolic 6-position) up to the number 11. This makes harmine 3-methyl-11-methoxy-beta-carboline. Some years ago the general term "tryptolines" was introduced to embrace the family of compounds with no methyl group on the 1-position. The numbering required that the pyridine nitrogen be called the 1-position, effectively maintaining the position numbers of the parent indoles, but it turns out that the original 1-position, now without a number, has to default to the end of the line, to the rather sad 9-position name.

Back to the individual chemical stories. This commentary will cover the scatter of beta-carbolines that might play some major role in the human nervous system, other than the harmine trilogy. Harmine, harmaline and tetrahydroharmine all have the oxygen at the 7-position, and mostly have their origins in the botanical world. The 6-position oxygen can come directly from serotonin or hydroxy-tryptophan, and are found both in plants and animals. Similarly, the hydrogen derivatives (unsubstituted) derive from tryptamine and tryptophan, again from both plants and animals.

6-Methoxytetrahydroharman (6-MeO-THH) is the title chemical of this recipe. This particular β-carboline is a focal point of an ongoing controversy. To put all the cards directly on the table, this compound can in theory be made easily in the body and thus it could be present as a normal component in the brain. It has been synthesized by McIsaac, in Texas, under physiological conditions, with acetaldehyde and 5-methoxytryptamine. And, so the reasoning goes, if it can be made under these conditions in the laboratory, why not in the brain? He was completely convinced that it would be found some day to play an important role in mental health, just as he was convinced that it would prove to be a psychoactive compound. Perhaps it would be the product of some psychological trauma, or maybe the source of such a trauma. He once told me (at a meeting years ago, over a quiet breakfast) that one of his ambitions was to assay the brains of people who were in all different kinds of mental states at the time of their deaths, and to correlate the carboline levels with that mental state. I asked him if he had personally tasted the material, and apparently he had not.

6-Methoxytetrahydro-β-carboline (6-MeO-THβC, pinoline) is a naturally occurring component of human blood and cerebral spinal fluid. Like 6-MeO-THH, it is readily formed from 5-methoxytryptamine, but with formaldehyde rather than with acetaldehyde. The levels have been found to be similar in schizophrenics and psychiatrically healthy patients, suggesting that it is not a factor in the chemistry of mental illness. It is a natural component of the human pineal gland and is quite effective in binding to serotonin sites in human platelets. It has been suggested that the balanced interplay between melatonin and pinoline in the manipulation of serotonin levels might be an explanation of the sleep/dream state. The carbolines just might play an endogenous role in creating dreams, our "asleep" visual tripping.

6-Methoxyharmalan (6-MeO-DHH) was the chemical intermediate in the synthesis given above. Its main claim for attention is that it is the immediate

result of the removal of a molecule of water from melatonin, which is a major actor in the biochemistry of the pineal gland. It is also a pretty effective monoamineoxidase inhibitor.

Harman is the simplest of the carboline alkaloids, and also one of the most widely distributed throughout the plant world. Many of its common names derive from these sources, such as loturine, aribine and passiflorin. In tasting trials with the alkaloid alone, there are no effects noted at even up to 250 milligrams orally. Rather surprising, even though it has been shown to be a good monoamineoxidase inhibitor, a 250 milligram trial followed in 20 minutes with 35 milligrams of DMT also had no effects. Clearly, harman does not share pharmacological similarities with its methoxylated cousins. Harman is the prototype alkaloid of the β-carboline class and has been found in many plants although not usually a contributor to the action for which they are best known.

It is a component of the bark of the legume *Arariba rubra* (*Sickingia rubra*), native to the Bahia state in Brazil, as well as from the bark of *Symplocus racemosa.* This tree was introduced into Goa in the mid-nineteenth century, and from it has come a drug called Araroba powder (or Goa Powder, Brazil powder, or Ringworm powder). This turn of the century drug of commerce contains the non-nitrogenous anthracene Chrysarobin, isolated commercially from the closely related legume, *Andira araroba* (*Vouacapoua araroba*). It has been used in the treatment of ringworm and a number of skin diseases. Harman plays no part in this medical use. I have not been able to pin down just why harman has been given the name Loturine. Some Genus, no doubt, but I don't know what it is.

It is, however, a recognized component of the extracts of the passion flower *Passiflora incarnata*, but the much more plentiful inventory of flavinoids present in this marvelously named plant seem to be the agents that are responsible for its sedative properties. Again, harman is probably not an active contributor to the reported pharmacological action. In fact, it has been spotted as a component of cigarette smoke, and here it certainly cannot be a factor that contributes to the virtues of smoking.

Tetrahydroharman (1-methyl-1,2,3,4-tetrahydro-β-carboline) has been the topic of many animal studies, but within the last few years it has demanded attention in an unexpected way. A couple of years ago there was a rash of medical problems that occurred and that were ascribed to an impurity found in certain supplies of the amino acid tryptophane. The chemical twist is that the causal impurity appears to be the product of cyclizing tryptophane with acetaldehyde. The product of this reaction is 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (tetrahydroharman-3-carboxylate, THH-3-COOH). It has been generated in experiment animals which have been fed tryptophane, ethanol, and cyanamide (a drug that, by interfering with the normal metabolism of alcohol, allows an accumulation of acetaldehyde in the body). The introduction of a new chiral center into an already asymmetric system gives promise of a challenging research problem, involving, in

any body fluid assay, an interesting analytical problem. Anyway, this amino acid decarboxylates to give tetrahydroharman, which was under some suspicion as being involved. Well, it wasn't involved, and the story itself has been discussed in the recipe for tryptamine. It is a story of politics, not of chemistry. Another 3-carboxylic acid derivative, the totally aromatic material without the 1-methyl group, has been found as a natural material in trace amounts in human urine. In fact, the yield was a total of 1.78 milligrams from 1800 liters. This is the ethyl ester of βC-3-carboxylic acid. It is an extraordinarily potent inhibitor of brain benzodiazepine receptors but, surprisingly, totally without any affinity for serotonin receptors. The hydrogenated version, THβC-3-COOH, as well as the harman analogue above (THH-3-COOH) are normal components of both beer and wine, being present at the several ppm level.

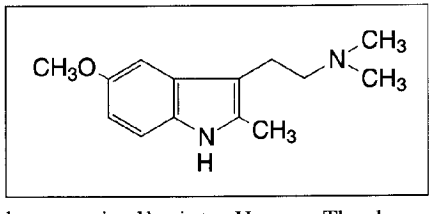
Since tetrahydroharman can come from the union of tryptamine and acetaldehyde, and since both of these compounds are natural components in the body, it is not surprising that tetrahydroharman is also a natural body factor. And, since ethanol is metabolized by way of acetaldehyde, the body level of tetrahydroharman closely reflects the amount of alcohol that has been consumed. A parallel reaction takes place in the human body between acetaldehyde and the neurotransmitter serotonin. This material, **6-tetrahydroharmol**, or 5HMTLN (5-hydroxy-9-methyltryptoline) employing the cute tryptoline nomenclature, also reflects alcohol consumption. The levels are, however, unreasonably high for the amount of free acetaldehyde normally adrift in the sober body and so it is suspected of having an alternate synthetic origin, perhaps involving pyruvate. The positional isomer with the hydroxyl group at the 7-position, **tetrahydroharmol**, is noteworthy for two reasons. A minor one, to let it be known that it, too, as with almost all possible combinations of natural tryptamines and aldehydes and acids looked for with diligence and sufficient sensitivity, has been found in human urine. The more impressive item: The use of the "tryptoline" word. Here is a view of an extreme cul-de-sac that was created by this procedure. This is all taken directly from the mass spectroscopy paper published in 1986. The problems arose from the fact that the methyl group of the harmine/harman world could not be slipped into the name, as its position had no logical number. And that there was no abbreviation for tryptoline that could be distinguished from tryptamine. Either could be "T." The paper discussed the hydroxylation metabolism of MTLN (methyltryptoline, in reality tetrahydroharman) to give the 6- and 7-hydroxylated derivatives. I would call these 6-tetrahydroharmol and tetrahydroharmol. But in this research paper, having been committed to the tryptoline word, these metabolites came out as 5HMTLN and 6HMTLN. The "5" and "6" represent the 6 and 7 positions on the carboline ring. The "H" is the hydroxyl group. The "M" is the methyl group which they do not choose to locate, but in the only offered numbering system it would be in the 9-position. And, of course, TLN is the abbreviation for tryptoline (MT was spelled methtryptoline in the title). I do believe that 6-H-9-M-TLN is harder to understand than tetrahydroharmol.

Serotonin, in an enzymatic interaction with the methyltetrahydrofolate one-carbon source, gives rise to the beta-carboline analogue, **6-HO-THβC**. This happens also to be the plant alkaloid plectomine as well as a metabolite of THβC in the rat. Attempts to make DMT from methyltetrahydrofolate and N-methyltryptamine (NMT) gave rise exclusively to the carboline 2-Me-THβC.

Tetrahydro-β-carboline (THβC, tryptoline) has also been demonstrated as being formed in the brain by the simple fusion of tryptamine with formaldehyde from methyltetrahydrofolate, and it is a normal component of human urine. It is the structural icon of the family of tetrahydro-β-carbolines without the methyl group at the 1-position, the "tryptolines," mentioned above. It, and the 2-methyl homologue mentioned just above, are both natural metabolites of DMT. I had the lucky timing to be present at a seminar at the Department of Pharmacology, at the U.C. Medical School in San Francisco, when the crowd from Stanford came up to give the first San Francisco unveiling of the "tryptoline" word. I remember that I was not the only chemist in the audience who groaned at the use of a totally unneeded and artificial name. But these researchers did a lot of work and a lot of publishing, and the term is now pretty well established in the literature. A cautionary note is appropriate here. It is essential, in abbreviating this material as THβC that the "beta" be included. Without it, the code "THC" will be assumed immediately to stand for tetrahydrocannabinol, the active component of marijuana.

#45. 5-MeO-TMT; TRYPTAMINE, 5-METHOXY-2,N,N-TRIMETHYL; INDOLE, 3-[2-(DIMETHYLAMINO)ETHYL]-5-METHOXY-2-METHYL; 5-METHOXY-2,N,N-TRIMETHYLTRYPTAMINE; 5-METHOXY-2-METHYL-DMT; 3-[2-(DIMETHYLAMINO)ETHYL]-5-METHOXY-2-METHYLINDOLE; INDAPEX

SYNTHESIS: To a stirred solution of 7.16 g of 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (indomethacin) in 150 mL $CHCl_3$ there was added, dropwise, 4.4 mL oxalyl chloride and the reaction mixture held under reflux conditions for 2.5 h. Removal of the solvent under vacuum produced a thick yellow oil which was dissolved in 150 mL of CH_2Cl_2. There was then added, in small portions, 40% aqueous dimethylamine until the aqueous phase remained basic to pH paper. The phases were separated, and the organic phase was washed sequentially with H_2O, dilute HCl, and finally saturated saline, then stripped of solvent under vacuum. The residue was dissolved in 20 mL EtOAc and after a few minutes, the product



crystallized out. This was recrystallized from a hot acetone/H_2O mixture yielding, after filtration and air drying to constant weight, 5.08 g 1-(p-chlorobenzoyl)-5-methoxy-2,N,N-trimethylindole-3-acetamide as pale yellow, fine needles.

To a suspension of 5.0 g of 1-(p-chlorobenzoyl)-5-methoxy-2,N,N-trimethylindole-3-acetamide in a mixture of 80 mL IPA and 20 mL H_2O there was added 1.0 g KOH and the mixture was stirred at room temperature for 1.5 h. The starting material gradually dissolved over this period. The excess IPA was removed under vacuum, and the residue partitioned between EtOAc and H_2O. The organic phase was separated, then washed sequentially with H_2O, dilute HCl, H_2O and finally saturated brine. After drying with anhydrous Na_2SO_4, the evaporation of the solvent yielded a white product that was recrystallized from a small quantity of boiling EtOAc that was allowed to cool slowly. There was obtained, after filtration and air drying, 1.44 g of 5-methoxy-2,N,N-trimethylindole-3-acetamide as white crystals.

To 40 mL of stirred anhydrous THF in a round-bottomed flask equipped with a reflux condenser and in an atmosphere of argon, there was added 2.70 g 5-methoxy-2,N,N-trimethylindole-3-acetamide. There was then added 20 mL of 1.0 molar $LiAlH_4$ in THF (there was a rapid evolution of bubbles) and the reaction mixture was held at reflux conditions for 2.5 h. The mixture was cooled to room temperature and treated with 8 mL of a 1:1 solution of IPA and H_2O. There was then added 2.0 mL 15% aqueous NaOH followed by an additional 2.0 mL H_2O. The suspension was filtered, the solids washed with 2x20 mL THF, the filtrate and washings combined, and the solvent removed under vacuum. The solid residue was dissolved in 25 mL 0.5 molar HCl, washed with CH_2Cl_2, made basic with 25% aqueous NaOH, and extracted with 3x40 mL CH_2Cl_2. Removal of the solvent under vacuum yielded a light yellow oil. This was distilled at 0.25 mm/Hg to yield a fraction boiling at 155-160 °C, weighing 1.52 g that was a pale yellow oil. This slowly set up as a milky crystalline solid, 5-methoxy-2,N,N-trimethyltryptamine (5-MeO-TMT) which had a mp of 90-92 °C.

DOSAGE: 75 - 150 mg, orally

DURATION: 5 - 10 h

QUALITATIVE COMMENTS: (with 65 mg, orally) "I felt the first intoxication at an hour. I was relaxed along with subtle day-dreaming to "Hearts of Space" music. I was sexually stimulated, with some heightening of intensity of orgasm. At the three hour point I seemed pretty much baseline. The rest of the day went without difficulty."

(with 90 mg, orally) "This was ingested in a capsule. Effects were first noted at 55 minutes with a feeling of relaxation and a mild impairment of fine motor skills. Sexual activity was initiated at the 90 minute point. Spinal tingles were felt

and, although erection may have been slightly more difficult than normal to maintain, orgasm was phenomenal. This potentiation was confirmed three more times over the next three hours! Mild stomach fullness was felt but no other GI problems were noted. Significant appetite suppression was noted for the first five hours, after which food tasted fine. Music evoked closed-eye drifting of thoughts but no true visuals occurred with eyes open or closed. A faint tremor of the jaw and fingers could be noted with careful examination. The effects were barely noticeable at the five hour point, and were completely gone at seven hours. Sleep was broken by awakening every few hours with moderate thirst, and dream activity seemed enhanced. There were no side-effects the following morning."

(with 120 mg, orally) "Unlike what I was told might happen, no sexual feelings were even remotely felt at any time during this experience. Thoughts seemed poorly connected and there was a feeling of being drugged with a sedative. Moderate chills and cold sensations occurred for several hours, requiring first a jacket and later a heating blanket. Time seemed moderately slowed and both respiration and pulse were reduced. Mild stomach fullness was noted, with indigestion. I was not hungry. No other GI problems occurred. Everything faded at about the five hour point, when I got very hungry and thirsty. My sleep was not comfortable, and the next morning I was still a little bit jittery."

(with 150 mg, orally) "No effects were felt until the 55 minute point, when a mild degree of intoxication began. At seventy minutes mild nausea and gastric fullness was apparent. There was a loss of fine motor skills and I found it hard to walk. My peripheral visual field had a waviness to it. Both television and a radio talk show became completely uninteresting and difficult to follow, and a feeling of sadness and despair became overwhelming. No music could change these feelings, although there definitely were pronounced closed-eye visuals by the 100 minute point. Emotions were extremely labile, going from profound crying to calm and back in a period of twenty minutes. I saw every defect and failure in my life and, although very sad, I recognized some things that I will correct in the future. Apparent body temperature fluctuations were continuous, going from being hot to chilled over and over again (actual body temperature was not measured). It was impossible to get comfortable for several hours. The stomach distress continued throughout the entire experience, with a moderately severe stomach ache during the third and fourth hours.

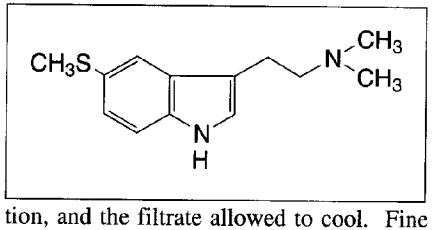
"By the sixth hour I could again watch television, and I did so while waiting for the experience to end. Some residual effects were still present at nine hours, but sleep thereafter was uneventful. No eating, or even drinking of water, was possible until the eighth hour, at which time small sips of water were tolerated. I awoke several times during the night and took in additional small amounts of water, but still arose the next morning very dehydrated. There were no other apparent hang-over effects."

EXTENSIONS AND COMMENTARY: This is certainly a hallucinogenic at a dosage of 150 mg orally, and can be compared with 300 mg of mescaline hydrochloride. This exact same chemical, if you were to remove that tiny, little, itty-bitty methyl group at the indolic 2-position, would become the remarkably potent material 5-MeO-DMT. But this latter stuff must be smoked or injected to show any activity at all. It is known that a methyl group on the alpha-carbon of a tryptamine blocks access of a deaminating enzyme allowing oral activity. I wonder if the methyl group on the 2-position is doing the same job of getting in the way.

At modest dosages in the 70-80 mg area orally, 5-MeO-TMT is both relaxing and sexually stimulating. The highest dosages studied seem to reveal a toxic component, and few subjects chose to repeat these levels.

#46. 5-MeS-DMT; TRYPTAMINE, N,N-DIMETHYL-5-METHYLTHIO; INDOLE, 3-[2-(DIMETHYLAMINO)ETHYL]-5-METHYLTHIO; N,N-DIMETHYL-5-METHYLTHIOTRYPTAMINE; 3-[2-(DIMETHYLAMINO)ETHYL]-5-METHYLTHIOINDOLE

CHEMISTRY: To a solution of 5.0 g of 5-methylthiotryptamine as the free base (the hydrochloride, with mp 252-254 °C or 263-265 °C, is dissolved in H_2O, made basic with aqueous NaOH, extracted with CH_2Cl_2, and the solvent removed under vacuum) in 250 mL MeOH, there was added 4.0 g $NaHCO_3$ and 6.8 g MeI. This



was held at reflux for 72 h, with the addition of 1.5 g more MeI at both 24 and 48 h. Removal of the volatiles under vacuum produced a white residue which was dissolved in 300 mL boiling EtOH, insolubles were removed by filtration of the hot solution, and the filtrate allowed to cool. Fine white crystals appeared which were removed by filtration, and air-dried to produce 3.22 g (53%) of N,N-dimethyl-5-methylthiotryptamine methiodide with a mp 177-179 °C.

A suspension of 3.0 g N,N-dimethyl-5-methylthiotryptamine methiodide in 50 mL DMF was treated with 1.9 g 1,4-diazobicyclo[2.2.2]octane and held at reflux for 3 h. The reaction mixture was diluted with 300 mL H_2O, extracted first with 200 mL EtOAc followed by 400 mL benzene. These extracts were combined and back-extracted with 10% HCl. This aqueous phase was made basic with 5N NaOH, and extracted with several portions of EtOAc. The organic extracts were pooled, dried with $MgSO_4$, and the solvent removed under vacuum to give a residue that was a dark gold oil. This was distilled at the KugelRohr to give a fraction that boiled at 130-140 °C at 0.01 mm/Hg which was a yellow solid, with mp 94-97 °C.

This was recrystallized from benzene/petroleum ether to give 1.41 g (76%) N,N-dimethyl-5-methylthiotryptamine as colorless needles, with a mp 97-100 °C.

DOSAGE: 15 - 30 mg, smoked

DURATION: < 1 h

QUALITATIVE COMMENTS: (15 mg, smoked) "Consumed it over 75 seconds, 15 seconds later I noticed it. Light, no visual, rather pointlessly stoned. In another 5 minutes I am starting to clear, and in another 5 I am repaired."

(with 20 mg, smoked): "Coming on very fast, quite intense, and within half an hour I am clear. I suspect 30 mg would be effective."

EXTENSIONS AND COMMENTARY: Sulfur lies in the very same column of the periodic table as oxygen, in the location directly below it. Therefore there are many similarities as to chemical bonding, making things like thioethers which are true analogues of ethers. A sulfur atom is put between two carbons rather than an oxygen atom. But the polarity and lipophilicity properties are different and the pharmacology is, of course, different. In the phenethylamine series, as reported in *PIHKAL*, there can be a considerable increase in potency: with the basic skeleton of 2,5-dimethoxyamphetamine, the replacement of a 4-methoxy group (giving TMA-2, active level 20-40 mg) with a 4-methylthio group (giving Aleph-1, active level 5-10 mg). The corresponding change for the ethyl counterparts (from MEM to Aleph-2) is an increase from an active level of 20-50 mg to one of 4-8 mg.

The 5-position on the indole ring of the tryptamine family is analogous to the 4-position in the phenethylamine family. And yet, here, with the 5-methoxy group of 5-MeO-DMT being replaced with the 5-methylthio group of 5-MeS-DMT, the activity actually seems to decrease by a factor of two, rather than increase by a factor of four. Is this a generality of the tryptamines, or is this an anomaly of this one pair of compounds?

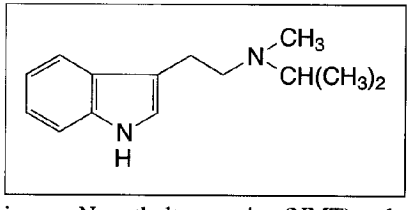
There is the raw stuff potentially available to answer this question. There are a couple of compounds known with the sulfur in the 4-position, which is the location of the oxygen atom in psilocybin. The 4-thio analogues have been synthesized from 4-methylthio-indole, via the oxalyl chloride method and reaction with the appropriate amine. With dimethylamine, the indoleglyoxylamide was made in a 43% yield and had a mp 163-164 °C. With diisopropylamine, the amide was made in a 27% yield and had a mp 190-192 °C. The final amines were prepared by the reduction of these amides with LAH in THF. N,N-Dimethyl-4-thiotryptamine (4-MeS-DMT) was obtained in a 68% yield and melted at 108-110 °C; N,N-diisopropyl-4-methylthiotryptamine (4-MeS-DIPT) was obtained in a 61% yield and melted at 92-94 °C. In animal studies of behavioral disruption with these three compounds, there was systematic drop of potency in going from the 5-MeS-DMT to 4-MeS-DMT to 4-MeS-DIPT.

The challenge would be to see what the activities would be in man. And, of course, to make a direct comparison to the oxygen counterparts. The 5-MeO-DMT has already been mentioned, and the remaining two would be 4-MeO-DMT and 4-MeO-DIPT. The former is a known compound but has not been measured in man. The latter is not a known compound.

#47. MIPT; TRYPTAMINE, N-ISOPROPYL-N-METHYL; INDOLE, 3-[2-(ISOPROPYLMETHYLAMINO)ETHYL]; N-ISOPROPYL-N-METHYLTRYPTAMINE; 3-[2-(ISOPROPYLMETHYLAMINO)-ETHYL]INDOLE

SYNTHESIS: (from tryptamine via NMT): A solution of 3.36 g tryptamine in 50 mL toluene was combined with another solution containing 5.52 g K_2CO_3 in 50 mL H_2O and vigorously stirred at room temperature. To this there was added, dropwise, a solution of 3.0 mL benzyl chloroformate in 20 mL toluene. Stirring was continued for 15 h, then the reaction was treated with 200 mL EtOAc, the organic layer separated, and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum, and the solid residue recrystallized from Et_2O/hexane to give 5.25 g (85%) N-(benzyloxycarbonyl)tryptamine with a mp of 84-86 °C. Anal: C,H,N.

A suspension of 0.76 g LAH in 50 mL anhydrous THF was stirred under an inert atmosphere, and treated with the dropwise addition of a solution of 2.27 g N-(benzyloxycarbonyl)tryptamine in 30 mL THF. The reaction mixture was held at reflux for 40 min, then cooled to 40 °C and the excess hydride destroyed with the addition of 50% aqueous THF. The solids were removed by filtration, washed with THF, the filtrate and washings combined, and the solvent removed under vacuum. The residue was impure N-methyltryptamine (NMT) and could be used without purification in the following alkylation. The isolation, purification and characterization of this intermediate amine is described in the NMT recipe, and of course the pure NMT can be used in the following reductive alkylation.



The crude N-methyltryptamine obtained above (for which one can substitute 1.20 g of pure NMT, as described in the NMT recipe) was dissolved in 50 mL EtOH, treated with 1.0 mL acetone, then with 0.5 g 10% Pd/C, and the reaction mixture shaken under a H_2 atmosphere at 50 psi for 15 h. The catalyst was removed by filtration through a bed of Celite, the filtrate was stripped of solvent under vacuum, and the solid residue recrystallized from Et_2O/hexane to give 0.93 g

N-isopropyl-N-methyltryptamine (MIPT) which had a mp 82-83 °C. From the benzyloxycarbonyltryptamine, the yield was 56%. From NMT the yield was 62% of theory. Anal: $C_{14}H_{20}N_2$. C,H,N. MS (in m/z): $C_5H_{12}N^+$ 86 (100%); indolemethylene$^+$ 130 (10%); parent ion 216 (2%). Efforts to isopropylate NMT with an excess of isopropyl iodide in IPA gave a 51% yield of a distilled product that did not crystallize.

(from N-isopropyltryptamine, NIPT): A solution of 0.47 g of N-isopropyltryptamine hydrochloride in 50 mL H_2O was made basic with 5% aqueous NaOH, and extracted with 3x40 mL CH_2Cl_2. The pooled extracts were stripped of solvent and the solid residue was dissolved in 25 mL IPA and treated with 0.35 g CH_3I. After 3 h at reflux, an additional 10 mL IPA and 0.14 g CH_3I were added and the reflux continued for 6 h. After removal of the solvent under vacuum, the residue was partitioned between dilute base and CH_2Cl_2. Removal of the solvent under vacuum yielded 0.29 g of an oil that was shown chromatographically to be a mixture of NIPT and MIPT in a 3:2 ratio. This was treated with 0.35 g CH_3I in 25 mL IPA and allowed to stand at room temperature for several days. A small quantity of crystals separated (N,N-dimethyl-N-isopropyltryptammonium iodide) which were removed by filtration. The filtrate was stripped of solvent under vacuum, and the residue again partitioned, as above, between aqueous NaOH and CH_2Cl_2. After removing the organic solvent, the residue (0.23 g NIPT to MIPT ratio 2:3) was treated with 0.5 g acetic anhydride, heated on the steam bath for 1 h, diluted with 5% aqueous NaOH and stirred for 2 h. This was extracted with 3x40 mL CH_2Cl_2, the extracts were pooled, and then extracted with 3x40 mL 1 N H_2SO_4. The pooled acid extracts were made basic with NaOH, reextracted with CH_2Cl_2 which, on pooling and the removal of the solvent under vacuum, gave 0.12 g of a colorless oil. Distillation at 0.1 mm/Hg (140-150 °C) gave 0.06 g (a 15% yield) of N-isopropyl-N-methyltryptamine as a colorless oil that spontaneously crystallized.

DOSAGE: 10 - 25 mg, orally

DURATION: 3 - 4 h

QUALITATIVE COMMENTS: (with 5 mg, orally) "Maybe a hint towards the end of an hour. Nothing further. Slept soundly."

(with 10 mg, orally) "There is no question but that this is active. I felt it just a half hour after taking it, and was somewhat disappointed to see it disappear over the next couple of hours. A very good feeling, quite randy."

(with 10 mg, orally) "Definitely active, mild excitement, dry mouth, some muscle tension in the back of the neck. At 75 minutes, definitely rolling, but still no visual effects. Finally subsiding. Not unpleasant, although a feeling of restlessness persists. Tailing insomnia for 6-8 hours."

(with 20 mg, orally) "My handwriting is shot. There are almost no visuals,

so why am I at a plus two? I feel very alert. Tried to sleep and ended up talking for quite a while instead. The overall experience can best be described as 'mild.'"

(with 25 mg, orally) "Quite an active dose. Same initial effects as with 10 milligrams, but considerably more excitement, central stimulation. At an hour, the effects seem to have plateau'd. Enhancement of visual field, i.e., brightened colors, clearly defined objects. Definite auditory effects, and I can pick out each sound with clear definition. Very 'heady,' but still remarkably free of visual distortion. Slight mydriasis. As it subsides, there is some muscle tension in the jaws, but much milder than with MDA or even psilocin."

(with 20 mg, by insufflation) "Immediate onset (less than a minute) and to ++. A little dizziness. My first thought is, 'This is definitely psychedelic.' Everything looked brighter, and vision was tinted orange. Everything appeared as if under an orange overlay. No other visual changes to speak of. Skin, hearing, sensitive. All-in-all, however, sensory changes were minor. The effects on thought were more typically psychedelic. The spin-offs, tangents, and implications of different threads of thought became apparent, and I could watch them unfold with my mind's eye. These effects gradually tapered off over the next three and a half hours or so. During this time, interaction with my companions was facile, and we had a good conversation. This compound seems to emphasize 'psychedelic' effects over 'hallucinogenic' effects."

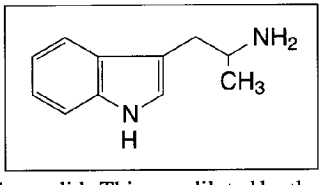
EXTENSIONS AND COMMENTARY: This is the simplest tryptamine with the somewhat magical pair of nitrogen substituents, a methyl group and an isopropyl group. Why should this combination allow a molecule to be orally active, even though the conventional thinking is that if there is a methyl group there, the amine oxidases will destroy it? My sense is that it is the N-small-group that does the job in the brain, and it is the N-big-group that keeps the inactivating oxidase enzymes away from the nitrogen atom. This is consistent with the N,N-dimethyl compound (DMT) not being orally active. Lying midway between DMT and DIPT is the ethyl compound, N-ethyl-N-methyltryptamine, or MET. It can be made by adding ethyl acetate to a reaction mixture where the formamide of tryptamine (see under NMT) has been reduced to NMT but there is still a goodly excess of hydride still remaining. The free base, as an oil, shows oral activity in the eighty to one hundred milligram range, so going from a methyl to an ethyl does indeed protect the compound from total enzymatic annihilation when taken orally.

The isomer of MIPT, with a considerably less bunched-up propyl group, is N-methyl-N-propyltryptamine, or MPT. This was made via the amide from indoleglyoxyl chloride and methylpropylamine, and reduction with LAH. MS (in m/z): $C_5H_{12}N^+$ 86 (100%); indolemethylene$^+$ 130 (8%); parent ion 216 (1%). Several human trials, up to twenty milligrams orally, showed no effects of any kind, so the activity, if there is any, is definitely less than that of MIPT. So the lumpiness of the isopropyl may be playing some role. There is no other way that is obvious of challenging this without adding more carbon atoms, and that would introduce another variable. This same decoration scheme has been used successfully in several other tryptamines in this story.

A couple of points of passing interest. As to stability: many of the free-base tryptamines are sensitive to air oxidation, some of them extremely so. This particular base, standing for a goodly number of years with no particular protection from air, has remained almost colorless, with no apparent signs of decomposition. And as to subjective effects: there is almost a total lack of visual phenomena. There were no wave-forms, color distortion or object shape changes, and no eyes-closed imagery, unlike most N,N-disubstituted tryptamines.

#48. α-MT; TRYPTAMINE, ALPHA-METHYL; INDOLE, 3-(2-AMINOPROPYL); ALPHA-METHYLTRYPTAMINE; 3-(2-AMINOPROPYL)INDOLE; IT-290; 3-IT

SYNTHESIS: There was prepared a solution of 25.75 g indole in 100 mL DMF. A second solution was also prepared by cooling 80 mL DMF in an external ice bath (internal temperature about 12 °C), stirring well, and adding 20 mL $POCl_3$ dropwise over the course of 30 min. This was then warmed to 25 °C and the first solution of indole in DMF was added, dropwise (with continued stirring), over an additional 30 min. Stirring was continued for yet another 45 min, during which time the temperature was raised to 40 °C. Yellow solids formed during this period. The reaction mixture was poured onto chipped ice, which produced a clear red solution. This was made basic with the addition of 200 mL 5 N NaOH, which allowed the separation of a yellow solid. This was diluted by the addition of 200 mL hot H_2O and, after cooling again, the product was removed by filtration and washed with cold H_2O. This can be recrystallized from aqueous DMF to yield, after air drying, 24.5 g (84%) of indole-3-carboxaldehyde as faint orange needles.



A solution of 4.35 g indole-3-carboxaldehyde in 17.2 mL nitroethane was treated with 0.77 g ammonium acetate and heated, with occasional swirling, on the steam bath for 2.5 h. The excess reagent was removed under vacuum and the resulting yellow solids washed with H_2O and air dried. Trituration under 25 mL dry MeOH, filtration, and air-drying gave 5.22 g (86%) 1-(3-indolyl)-2-nitroprop-1-ene as a yellow powder with mp 190-192 °C.

A suspension of 10.7 g LAH in 100 mL anhydrous THF was placed under an inert atmosphere, stirred, and treated, dropwise, with a solution of 10 g 1-(3-indolyl)-2-nitroprop-1-ene in anhydrous THF over the course of 2.5 h. The reaction mixture was brought to reflux temperature, held there for 2 h, and then returned to

room temperature. The excess hydride was destroyed with an aqueous THF solution (80 mL of 25% solution) and there was then added 10 mL of 50% NaOH. There was added 150 mL Et_2O, and the stirring was continued until no more solids formed. The reaction mixture was filtered and the filter cake washed with 150 mL Et_2O. The filtrates and washings were combined, dried over K_2CO_3, and the solvent removed under vacuum. The residue weighed 9.2 g and was distilled at 130-140 °C at 1 mm/Hg to give a white oil that crystallized and had a mp of 96-98 °C. This was recrystallized from an ethyl acetate/petroleum ether mixture, and had a mp of 97-100 °C. The yield was 6.3 g (73%). IR (in cm-1): 750, 818, 911, 933, 1093, 1111. MS (in m/z): $C_2H_6N^+$ 44 (100%); indolemethylene$^+$ 130, 131 (44%, 43%); parent ion 174 (2%). A sample dissolved in 10 volumes of methanol, treated with one equivalent of glacial acetic acid, and taken to dryness under vacuum gave the acetate salt which, on recrystallization from ethyl acetate and air drying to constant weight, yielded the product α-methyltryptamine (α-MT) as fine white crystals with a mp of 143-144 °C. The fumarate salt, formed by the addition of ethyl acetate to a hot solution of free base α-MT in methanol which had been neutralized with fumaric acid, was isolated as fine white needles with a mp of 200-203 °C.

DOSAGE 15 - 30 mg, orally;
5 - 20 mg, smoked

DURATION 12 - 16 h

QUALITATIVE COMMENTS: (with 15 mg, orally) "I got a strong psychedelic experience that lasted about twelve hours, but an unexpected relief from my chronic depression that lasted for four days."

(with 20 mg, orally) "Nothing happened for three hours — I thought I had drawn a blank. Then I became a little uncomfortable, restless, this delayed action is new to me. I feel completely washed out, exhausted. And I had a hangover the next morning."

(with 30 mg, orally) "It felt a little like speed, strong speed. Yet I found myself yawning and in sort of a dreaminess state and quite lethargic. It lasted a long time."

(with 30 mg, orally) "Effects were first noted in just over an hour, a general numbness and a mild loss of motor coordination. This all became more pronounced over the next half hour, but my thoughts remained clear. A hand tremor and jaw tightness persisted throughout the experience. Music was OK but I didn't really connect with it. There were no open or closed-eye visuals, but there was a moderate light sensitivity that lasted the day, and the visual field was altered such as the outside world did indeed appear unreal and alien. Were there any positive aspects to the day? I talked with a friend for two hours on the telephone, with ease. And I had no appetite. But there seems little else to recommend this compound. I slept well at the 12th hour."

(with 80 mg, orally) "I shot up in an hour, and by another hour I was vomiting worse than with mescaline. Absolutely no visuals, no hallucinations, but extreme depersonalization. Thirteen hours into this and it is still go, go, go. Out with a bit of pot."

(with 100 mg, orally) "There was pupillary dilation, jaw clenching, tachycardia and vomiting. Too much. But I really liked this compound at lower dosages."

(with 4 mg, smoked) "It burns and smells bad. It took quite a while to come on. After a half hour, BINGO, there was a very slow building of a definite psychedelic. It builds slowly but strongly for another few hours to a plateau at maybe four hours after which a very slow decline sets in. But even after 18 hours following input, and after 7 hours of sleep, I awoke still feeling the effects."

(with 5 mg, smoked) "Qualitatively it was milder and less intense than mushrooms, but much longer lived. Not complex, but just a lot of very good spirit, energetic feeling, enhanced colors, attractive rhythms in music. Party stuff."

(with 6 mg, smoked) "Onset was immediate, with heart racing, enhancement of surroundings. Taste? Pee-yew!"

(with 10 mg, smoked) "While there are no true visuals to speak of, the overall picture of things seemed grainy — as if filmed on low quality, color 16mm film. There is an energized eeriness about inanimate objects. This lasted three hours."

(with 20 mg, smoked) "I inhaled several hits from my vaporizer and sat back. I felt head-pressure and uneasiness, then suddenly I became very fast. My mind was moving fast, and my body was speeding along with it in an unconscious way. Several hours into it, I began to notice more of a psychedelic effect beginning to manifest. It seemed as if the speedy part was becoming less predominant and the psychedelic visual effects were starting to kick in. I went back to my room to watch the distinctive waves of soft red/orange visuals. They were similar to colors of LSD. It gradually increased to a level of intensity similar to perhaps 0.5 - 1.0 g *P. cubensis*, and after several more hours it was clear that I had reached the plateau. Feeling fairly tired and ready for bed, I decided to call it a night. Quite to my surprise, when I awoke four hours later I was at the same level as when I went to sleep. Gradually, over the next day, I returned to baseline and I was left feeling quite euphoric with a pleasant afterglow."

EXTENSIONS AND COMMENTARY: In the 1960's there was quite a bit of interest at a couple of pharmaceutical houses in the indole analogues of amphetamine. Both the alpha-methylated tryptamine (this compound, α-MT) and the alpha-ethylated homologue (α-ET, see its separate recipe) were found to be effective monoamine oxidase inhibitors, and both were clinically studied as potential antidepressants. The ethyl compound became a commercial drug, offered by the Upjohn Company as Monase, but now is considered to be without medical use and is a Schedule I drug. It is interesting that this methyl compound, α-MT was

also a medically available antidepressant in the Soviet Union in the 1960's and was sold under the name of Indopan, in 5 and 10 milligram tablets.

There is quite obviously a wide range of reported effects described for α-MT, indicating much individual variability. For some it has a fast onset, for others a slow one. Some find it a good psychedelic, others are disturbed by the negative physical side-effects. This is all a bit reminiscent of harmaline, where the spectrum of responses also range from 1 to 10 on a scale of 1 to 10. Perhaps this is a reflection of the monoamineoxidase inhibition property, and if so, perhaps low levels of α-MT might serve the harmaline role of inhibiting the metabolic destruction of DMT in some form of a pharmahuasca.

I have always been intrigued by a fascinating bit of speculation. Ken Kesey had his own nest in a log cabin down in La Honda, back in the '60's. This was given fame mostly by Tom Wolfe's *The Electric Kool-Aid Acid Test,* where it was well described. At that time, Kesey served as an experimental subject for a number of studies involving psilocybin, Ditran, and α-MT. Shortly after these were completed, he left and took the role of "The Chief" of his band of "Merry Pranksters" who traveled far and wide around the U.S. in the now famous bus, the "Further." I had heard as a rumor that the research supply of α-MT had disappeared at about the same time, and the thought occurred to me that maybe the drug consumed on the tour was not LSD but α-MT. I made gentle inquiry of the research director, whom I knew personally, if this might be so, and his opinion was that the material used by Kesey and the pranksters was probably LSD, as it was so widely available at that time.

There is another parallel to the ethyl homologue, α-ET. In the commentary under α-ET, I had mentioned how industry was benefiting economically in the War on Drugs, by charging inflated prices for reference and research samples. Here, there just might be political counterpart. There are several commercial sources for α-MT, with catalog prices ranging from $50 to $150 per gram. I bought a gram from Acros Organics and it was delivered with dispatch. I also received the MSDS sheet (Material Safety Data Sheet, a listing of physical hazard information now required to accompany all chemicals purchased) and it not surprisingly had no mention of any known hazard. Imagine my surprise when I received the invoice only to find that there was a $6 surcharge as a hazardous shipping charge. Some three 800-number phone calls later, I got to a person at Fisher Scientific who told me that this was a result of the State of California placing this compound on a Classification #110 listing. I had previously received solvents from Acros that were inflammable, volatile, bad smelling and rather toxic, and had never before had to pay a hazard fee. I suspect that someone in Sacramento has discovered that this compound has a wide acceptance as a stimulant and somewhat psychedelic, and is effectively capitalizing on it before it becomes illegal. One of the commercial suppliers, a mail-order operation called CRSB, provides drug precursors (not illegal) and actual drugs (not illegal) as long as no illegal use will be made of them. The demand for α-MT is very high, second only to gamma-butyrolactone which can be converted to GHB with sodium hydroxide (the #3 item in their sales volume listing).

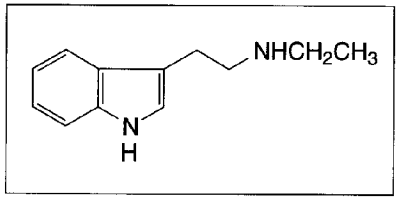
There is some interesting biochemistry and pharmacology all around the edges of α-MT. The 4-hydroxy analogue of α-MT has been looked at in human subjects. It is reported to be markedly visual in its effects, with some subjects reporting dizziness and a depressed feeling. There were, however, several toxic signs at doses of 15 to 20 milligrams orally, including abdominal pain, tachycardia, increased blood pressure and, with several people, headache and diarrhea. The 5-hydroxy analogue of α-MT is also a well-studied compound, but not, to my knowledge, in man. It can be called α-methylserotonin (α-M-5-HT or α-MS), and it is an effective inhibitor of 5-hydroxytryptophan decarboxylase, which is the immediate precursor to serotonin (5-HT). The amino acid tryptophan, without the 5-hydroxy group but with an α-methyl group, is α-methyltryptophan, and it is readily metabolized by the rat to α-MS. In the pineal, it mimics serotonin rather than melatonin, and there is no evidence that it is acetylated on to a melatonin analogue. This α-methyl blocking of the amine group from metabolic deamination represents a half-way step in the modification of serotonin to allow it to enter into the central nervous system, i.e., the protection of the amine group from deamination because of its alpha-methyl substituent. The rest of the needed modification is the methylation of the 5-hydroxy group as well. This yields alpha,O-dimethylserotonin which allows the entry of this serotonin-like product (α,O-DMS) directly into the brain. In all this casual use of the Greek letter alpha to indicate the carbon atom next to the nitrogen atom of the tryptamine side-chain, readers of the very old literature should remember that the letter alpha used to be used to indicate the 2-position of the pyrrole ring.

A few more compounds can be considered as part of this territory. The addition of a methyl group to the indolic 1-position gives rise to 1,α-DMT. This has been prepared from the 1-methylindole-3-carboxyaldehyde via the intermediate nitrostyrene reduced, in turn, with LAH. It represents the MLD-41 to LSD relationship, where there was some three-fold drop in potency. The alpha,alpha-dimethyltryptamine homologue (α,α-DMT) is also known. It represents the phentermine to amphetamine relationship where, again, there is a three-fold drop in potency. It would be a fair hypothesis to expect either of these "DMT's" to be active stimulants at reasonable dosages, but neither has been explored in man. The analogue with the methyl group relocated to the indolic 4-position (4,α-DMT) has been looked at in man. At an oral dose of 20 milligrams, there are reports of feelings of unreality. External body signs include flushing, muscle tightness, and eye dilation.

There are five possible chain relocations, from the normal 3-position to the 2-, the 4-, the 5-, the 6- or the 7-positions. All five "α-methyltryptamine" isomers are known, but only one is known to be active in man as a CNS active material. This is the 5-isomer, 5-(2-aminopropyl)indole or 5-IT, which, at 20 mg orally, is a long-lived stimulant producing increased heart-rate, anorexia, diuresis, and slight hyperthermia for about twelve hours.

#49. NET; N-ETHYLTRYPTAMINE; TRYPTAMINE, N-ETHYL; INDOLE, 3-[2-(ETHYLAMINO)ETHYL]; 3-[2-(ETHYLAMINO)ETHYL]-INDOLE

SYNTHESIS: (from indole) To a well-stirred solution of 1.6 g indole in 30 mL anhydrous Et_2O there was added, dropwise over the course of 30 min, a solution of 3.8 g (2.6 mL) oxalyl chloride in 30 mL anhydrous Et_2O. Stirring was continued for an additional 15 min, during which time there was the separation of indol-3-ylglyoxyl chloride as a yellow crystalline solid. This intermediate was removed by filtration and washed with Et_2O. It was used directly in the following step. This



solid acid chloride was added to 3.6 g anhydrous ethyl amine in Et_2O and stirred until the color had largely faded. Then there was added 100 mL of 2 N HCl. The mixture was cooled, and the resulting product N-ethylindol-3-ylglyoxamide was removed by filtration. The air-dried product was obtained in a 67% yield (mp 208-210 °C from benzene).

A solution of 1.6 g N-ethylindol-3-ylglyoxylamide in 50 mL anhydrous THF was added, dropwise, to 1.5 g LAH in 50 mL anhydrous THF which was well-stirred and under an inert atmosphere. This was brought to reflux and held there for 3 h. The reaction mixture was cooled, and the excess hydride destroyed by the cautious addition of wet THF. A 15% NaOH solution was then added until the solids had a loose, white cottage cheese character to them, and the mobile phase tested basic by external damp pH paper. These formed solids were removed by filtration, washed with first THF and then MeOH. The filtrate and washings were combined, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum. The residue set up to a crystalline mass. This was converted to the hydrochloride salt (mp 188-190 °C from benzene/MeOH) in a 35% yield.

(from tryptamine) To a well-stirred solution of 16.0 g tryptamine base in 25 g triethylamine, there was added, dropwise, 11.2 g acetic anhydride. The mixture was heated on the steam bath overnight, then the volatiles were removed under vacuum. The residue was dissolved in 100 mL CH_2Cl_2 and washed with 100 mL dilute aqueous HCl. The water phase was extracted twice with additional CH_2Cl_2, the organic phases were combined, washed with aqueous $NaHCO_3$ solution, and the solvent removed under vacuum. The resulting residue (12.5 g of a dark viscous oil) was distilled at the KugelRohr to give N-acetyltryptamine as a viscous amber oil boiling at 185-200 °C, which set to a fused glass at room temperature. It weighed 9.45 g, for a yield of 47% of theory. This glass-ground under hexane had a mp of 70-73 °C and formed white crystal from toluene, mp 73-74 °C. IR (in cm^{-1}) 756, 810, 1022, 1073, 1103, C=O at 1640. MS (in m/z): indolemethylene+ 130 (100%); 143 (86%); parent ion 202 (7%).

A solution of 2.31 g of N-acetyltryptamine in 30 mL anhydrous THF was

added, dropwise, to 60 mL of 1 M LAH in THF and held at a reflux under argon. After 12 h reflux, the reaction was returned to room temperature and the excess hydride destroyed by the addition of 20 mL of 50% aqueous THF. The mixture was filtered through paper, washed with 3x25 mL THF, and the combined filtrates and washings stripped of volatiles under vacuum. The remaining pale cream-colored oil was distilled at 0.1 mm/Hg to give a white oil, bp 125-135 °C, 1.58 g (73%). This free-base product spontaneously crystallized to a white, waxy solid, with a mp of 80-81 °C. IR (in cm^{-1}): 751, 887, 940, 1021, 1051, 1118. MS (in m/z): $C_3H_8N^+$ 58 (100%); indolemethylene$^+$ 131, 130 (48%, 33%); parent ion 188 (2%). N-ethyltryptamine base, dissolved in 5x its weight of IPA, acidified with concentrated HCl, and Et_2O added dropwise, yields the hydrochloride salt, N-ethyltryptamine hydrochloride or NET, with a mp of 181-182 °C. IR (in cm^{-1}); 750, 761, 825, 1020, 1108, 1142.

NIPT; TRYPTAMINE, N-ISOPROPYL; INDOLE, 3-[2-(ISOPROPYLAMINO)ETHYL]; N-ISOPROPYLTRYPTAMINE; 3-[2-(ISOPROPYLAMINO)ETHYL]INDOLE

SYNTHESIS: To a solution of 3.2 g tryptamine base in 25 mL IPA there was added 6.8 g isopropyl iodide and the solution was held at reflux for 36 h. All volatiles were removed under vacuum, and the residue suspended in dilute aqueous NaOH and extracted three times with 40 mL portions of CH_2Cl_2. These extracts were pooled and, after removal of the solvent, yielded 2.19 g of a dark oil which crystallized on standing. This was distilled at the KugelRohr at 130-150 °C at 0.08 mm/Hg to give 1.51 g of a white oil that set to a solid in the receiver. An analytical sample was recrystallized from IPA, and had an mp 94-95 °C. A solution of the free base in 10 mL warm IPA was treated with concentrated HCl, dropwise, until the solution was red to external damp pH paper. The spontaneous crystals that formed were diluted, with stirring, with 20 mL anhydrous Et_2O, the resulting curdy, crystalline mass removed by filtration, washed with additional Et_2O, and air dried to constant weight. Thus there was obtained 1.58 g N-isopropyltryptamine hydrochloride (NIPT) as fine white crystals, mp 224-227 °C. MS (in m/z): $C_4H_{10}N^+$ 72 (100%); indolemethylene$^+$ 131,130 (50%, 35%); parent ion 202 (2%). IR (in cm^{-1}): 751, 860, 1024, 1036, 1112.

EXTENSIONS AND COMMENTARY: Why two complete recipes, for two monoalkyltryptamines which have received only modest human trials but which have yet to have any active levels discovered? For several very good reasons.

First, these two monosubstituted tryptamines described here are easily made as pure entities, in acceptable yields.

Secondly, they are prepared here by completely different processes, each of which is amenable to modification to other, potentially useful mono-substituted tryptamines (NRT'S, where the R is a sizable alkyl group). There is the oxalylamine

route and the acylation route (used here with ethylamine for NET), and the alkyl halide route (used here with isopropyliodide for NIPT, but which proved to be rather useless in making NET, where the major product was the quaternary salt). With these two procedures available, there is almost no limit to the potential identity of that mono-group on the nitrogen atom of tryptamine. Quite a few have already been made. Let me list some examples.

The normal-propylamine NPT has been made by the oxalylamide route, with the amide having a mp 179-181 °C (75%) from benzene and NPT hydrochloride mp 186-187 °C (33%) from MeOH/benzene. An attempt to make NPT by the alkyl halide procedure failed. Using these same ratios of reactants, there was the formation of a sizable quantity of DPT with appreciable unreacted tryptamine presence (T:NPT:DPT/1:5:4). A recycling under the same conditions gave T:NPT:DPT/0:3:7 and a third cycle gave only DPT, but with a loss of almost 90% of the material, presumably to quaternary salt formation. Interestingly, NPT is less toxic than DPT in experimental mice, but has not yet been assayed in man.

NBT (N-butyltryptamine) is also an oxalylamide product. The amide has a mp 167-169 °C (81%) from benzene, and NBT hydrochloride has a mp 203-205 °C (13%) from benzene/MeOH.

The two geometric isomers, mono-isobutyl and mono-sec-butyl tryptamines are best called NIBT and NSBT. They also have been made by the oxalylamide route and the hydrochloride salts melt at 150-151 °C and 175-177 °C resp. Interestingly, NSBT is one of the two mono-substituted tryptamines that just might have CNS activity. It has shown a generalized and somewhat diffuse intoxication with several studies covering the 25 to 75 milligram range. Short lived, intellectual excitement with some modest sensory enhancements. Promising, but no plus three's, yet.

The tertiary-butyl analogue, NTBT, is the remaining mono-substituted tryptamine that just might have psychotropic potential. In the 5 to 20 mg area, there is a light-headed intoxication that is a totally pleasant buzz, but nothing more profound than that. Wouldn't it be fascinating if it turned out that all of the mono-tryptamines (the NRT's) were GHB-like intoxicants, and totally devoid of psychedelic activity? That would be a true challenge to the SAR crowd.

Both the mono-amyl and the mono-hexylamines have been described (NAT and NHT), both having been made by the glyoxylamide process. These, too, as has been mentioned above, appear to be inactive in man, as reported by Stephen Szara at the famous "Ethnopharmacologic Search for Psychoactive Drugs" conference, organized by the late Dan Efron of the National Institute of Mental Health, in San Francisco, in 1967.

Thirdly, this is where the staggering potential power of this recipe comes into focus. One can make, easily, pure mono-ethyl, mono-propyl, mono-isopropyl, mono-n-, s-, i- and t-NBT's. And using these directions, one can systematically react these mono's with every different alkyl halide. Thus, there suddenly becomes available "this" times "that" squared possibilities of new tryptamines, every one

easily made, every one potentially psychoactive, and almost every one totally unknown to the scientific literature. The oxalylamide process goes out to lunch when one considers the unlikelihood of finding N-s-butyl-N-i-butyl amine as a commercially available product. It is no longer required. Make IBSBT (how would you ever encode that product?) by the simple treatment of one of these mono's with an appropriate alkyl halide, and clean up the mess with a dash of acetic anhydride.

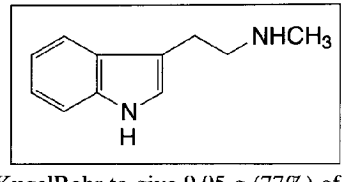
Fourthly, and most important, every one of these adventures has an exact counterpart with the inclusion of that magical 5-methoxy group. Whatever is found with the 5-H archetype is certain to be more potent, and correspondingly unpredictable, with a 5-methoxy-substituent. Some have already been made. Most have not. This is open territory. Go West, young man!

Back to the mundane. I really have to justify the "N" in the NET. I will try to hold to the convention that is expanded on at length in the recipe for DBT, that if there is one alkyl group (a monoalkyl tryptamine) then it is N-alkyl-tryptamine, with the reserving of M for methyl rather than for mono, even in the case of monomethyltryptamine. There is wide use of MMT for monomethyltryptamine in the literature, but the ambiguity comes from the higher mono-substituted homologues, and this makes NMT a much safer name. As there can be several places for the ethyl group, perhaps it is best to give the location as a number or letter, such as 1, 2, α (for alpha) or N.

A detail for spectroscopists amongst us. With the mono-N-substituted tryptamines, there is always a 131 e/m mass peak, larger than the 130 e/m mass peak. This peak is a minor one with the disubstituted analogue. The same relationship exists with the 5-methoxy analogues, where N-monosubstituted compounds have a 161/160 m/e fragment (the 5-methoxymethylene indole fragment), with the 161 m/e peak always the larger. The primary amine shows this same character. The disubstituted analogue has only the 160 m/e fragment.

#50. NMT; TRYPTAMINE, N-METHYL; INDOLE, 3-[2-(METHYLAMINO)ETHYL]; N-METHYLTRYPTAMINE; 3-[2-(METHYLAMINO)ETHYL]INDOLE

SYNTHESIS: A suspension of 10 g tryptamine base in 10 g butyl formate was held at reflux for 24 h. The resulting clear solution was stripped of volatiles under vacuum, and the residue partitioned between dilute HCl and CH_2Cl_2, and the aqueous phase extracted twice with additional CH_2Cl_2. The pooled organic extracts were washed once with dilute aqueous HCl, once with dilute aqueous NaOH, and the solvent removed under vacuum to give a black oil. This was distilled at the KugelRohr to give 9.05 g (77%) of



N-formyltryptamine as a clear oil, boiling at 170-190 °C at 0.1 mm/Hg which set to a glass. MS (in m/z): indolemethylene$^+$ 130 (100%); 143 (57%); parent ion 188 (15%). This amide slowly crystallized on standing, but was used as the glass in the reduction described below.

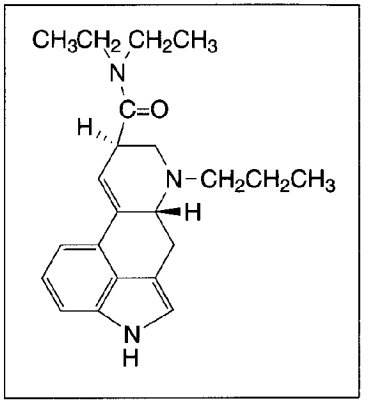
A solution of 1.88 g N-formyltryptamine in 40 mL anhydrous Et_2O was added to 60 mL of a 1 N solution of LAH in THF, well-stirred under argon, and was held at reflux for 24 h. After cooling to room temperature, the excess hydride was destroyed by the addition of 20 mL of 50% aqueous THF. The resulting solids were removed by filtration, and the filter cake washed repeatedly with damp THF. The basic filtrate was stripped of solvent under vacuum to give 1.39 g of a pale oil which started to crystallize. After distillation at 135-145 °C at 0.1 mm/Hg, there was obtained 1.22 g (70%) of N-methyltryptamine as a white oil which spontaneously set up to white crystals of the free base. These rapidly darkened on exposure to air. The IR (in cm^{-1}): 740, 1018, 1103, 1132, 1161. The literature mp is 90 °C. A 0.22 g sample of darkened base in 1.0 g IPA was neutralized with concentrated HCl (using external, moistened pH paper as a titration guide) with the development of an intense blue-green color with the addition of each drop of acid. The acidified solution (now a stable blue-green color) was diluted with diethyl Et_2O (about 1 mL). This cloudy solution, upon scratching, set to crystals which, upon removal by filtration, Et_2O washing, and air drying to constant weight, weighed 0.18 g and had a mp of 178-180 °C. N-methyltryptamine hydrochloride (NMT) IR (in cm^{-1}): 748, 850, 1009, 1104, 1119, 1136. MS (in m/z): $C_2H_6N^+$ 44 (100%); indolemethylene$^+$ 131, 130 (61%, 51%); parent ion 174 (2%).

EXTENSIONS AND COMMENTARY: N-Methyltryptamine (monomethyltryptamine, NMT) is an alkaloid that has been found in the bark, shoots and leaves of several species of Virola, Acacia and Mimosa. However, the major snuffs associated with these plant have been shown to also contain 5-MeO-DMT and are discussed there. NMT has been synthesized in a number of ways. One can react 3-(2-bromoethyl)indole with methylamine. NMT can be isolated as the benzoyl derivative from the methylation of tryptamine with methyl iodide followed by reaction with benzoyl chloride, with the hydrolysis of this amide with alcoholic KOH. It can also be synthesized from indole with oxalyl chloride, with the resulting glyoxyl chloride reacting with methylamine in ether to give N-methylindol-3-ylglyoxalylamide (mp 223-224 °C from IPA) which is obtained in a 68% yield. This is reduced to NMT to give the amine hydrochloride (mp 175-177 °C from EtOH) in a 75% yield. The most simple and direct synthesis is the formamide reduction given above.

To my knowledge there have been no reports of oral activity of NMT, although its wide availability from botanic sources has encouraged some explorers to assay it. I have had one report that the smoking of 50-100 mg gave visuals that lasted for maybe 15 seconds. The N-hydroxy analogue has been noted as being found in plants, in the "DMT is Everywhere" chapter.

#51. PRO-LAD; 6-NORLYSERGAMIDE, N,N-DIETHYL-6-PROPYL; 6-NORLYSERGAMIDE, N,N-DIETHYL-6-PROPYL; N,N-DIETHYL-NORLYSERGAMIDE, 6-PROPYL; 6-PROPYLNORLYSERGAMIDE, N,N-DIETHYL; 9,10-DIDEHYDRO-6-PROPYL-N,N-DIETHYLERGOLINE-8β-CARBOXAMIDE; 6-PROPYL-NOR-LSD

SYNTHESIS: To a solution of 66 mg nor-LSD (see under ETH-LAD for its preparation) in 2 mL freshly distilled DMF under a nitrogen atmosphere, there was added 48 mg anhydrous K_2CO_3 and 41 mg propyl iodide. When TLC analysis indicated that the nor-LSD had been consumed (9 h) all volatiles were removed under a hard vacuum. The residue was solubilized in $CHCl_3$ (5x5 mL) and the pooled extracts dried over anhydrous Na_2SO_4, cleared by filtration, and the solvent removed under vacuum. There was a residual white solid. This was separated into two components by centrifugal chromatography (alumina, CH_2Cl_2, nitrogen and ammonia atmosphere) the first of which was the major product. After removal of the solvent, this was dissolved in hot benzene, filtered and cooled. The addition of hexane prompted crystallization of N-propyl-nor-LSD (9,10-didehydro-6-propyl-N,N-diethylergoline-8β-carboxamide) as a crystalline product weighing 54 mg (72% yield dry). It had a mp of 87-88 °C.



DOSAGE: 100 - 200 micrograms, orally

DURATION: 6 - 8 h

QUALITATIVE COMMENTS: (with 80 µg, orally) "I am aware of some change within a quarter hour, and then nothing more for quite a while. Certainly no visuals, almost like MDMA in that I am not really sure that this is even psychedelic — it does not have any of the flavor of LSD. I want to try it at a higher dose some day."

(with 135 µg, orally) "A strange development into a sort of paranoia place, without any reasonable dialogue with my partner. A light-headed experience of a different kind, but we did not find common space. Not too comfortable — emotions are dull. At about mid-experience, considerable visuals came into play, with easy fantasy interlocking with music. Brüchner's "Viola quintette in A" produced extraordinary castle frames within castle walls. Emotions were reknit, food was good, and sleep fine at the 8th or 9th hour. It is not up to LSD (if that is your standard) because it is basically not <u>like</u> LSD."

(with 175 µg, orally) "This is an intellectually clear material, but it is a funny material. I am certainly at a +++ or at least I was a couple of hours ago. How does one describe PRO-LAD? It's not-quite-this and not-quite-that sort of stuff. Or, to borrow from Winnie-the-Pooh, 'It's not at the bottom, and it's not at the top (but this is the stair where I always stop)' — oh, never mind. I mean, I'm not sure how to categorize this material. It's pleasant, it's fine for fooling around, it's good for humor, even excellent. It's very good for clear thinking, although not cosmic-type particularly. It's a sort of nice, comfortable, middle-American, July-Fourth-Picnic, apple-pie with ice cream sort of psychedelic, the kind that you can wrap up in gold and white striped paper for your youngest aunt, the one who likes to think she's really a bit wild, you know — the kind of psychedelic that's a bit much for your Dad or Mom, but it's just jazzy enough to keep some younger relatives happy with you for a few months. However, I must tell you, kid, if you try to bring this to the Big Town, well... It is pretty much dropped off, now. Ah'm gonna lie mahself on down."

EXTENSIONS AND COMMENTARY: With success in the preparation of the rather stable nor-LSD intermediate, any number of 6-substituted nor-LSD homologues and analogues can be synthesized. Simply use the appropriate alkyl bromide or alkyl iodide and the desired product will be in hand, after a modest amount of rather sophisticated purification at a micro scale. Several analogues are in the chemical literature, and some of them have been explored in direct comparison to LSD. Here are a few examples:

N-Propynyl-nor-LSD (PARGY-LAD). Some activity at 160 micrograms. Active at 500 micrograms.

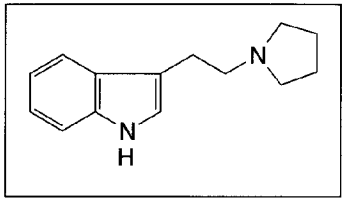
N-Butyl-nor-LSD (BU-LAD). Something at 500 micrograms.

N-Phenethyl-nor-LSD (PHENETH-LAD). Nothing at 500 micrograms.

As these substituents get heavier and heavier, the potency of the products drop by an order of magnitude or so, or even more. But here, in this N-substituted nor-LSD family, there is a fantastic research opportunity just waiting to be exploited, an exact parallel to the radio-iodine labeling of DOI as was described in PIHKAL. It is a good guess that this position is one of good metabolic stability. So what about putting on a small group that can be labeled with a reasonably long-lived positron isotope? A specific proposal: N-(2-fluoroethyl)-nor-LSD with an ^{18}F radio-label. The compound should be makable rather quickly (nor-LSD and $^{18}FCH_2CH_2I$ in DMF with potassium carbonate) and cleanly purified by centrifugal chromatography, all well within the almost two hour half-life considerations of radio-fluorine. Here is a group that would be (in theory) intrinsic to the central activity of the end product, N-(2-fluoroethyl)-nor-LSD. The end compound could be synthesized, purified, characterized and sterilized quickly, allowing its brain localization and central dynamics to be determined by PET scanning, with virtually no risk to the subject. Let's call it FLUORETH-LAD.

#52. pyr-T; TRYPTAMINE, N,N-TETRAMETHYLENE; INDOLE, 3-[2-(1-PYRROLIDYL)ETHYL]; PYRROLIDINE, 1-[2-(3-INDOLYL)ETHYL]; N,N-TETRAMETHYLENETRYPTAMINE; 1-[2-(1H-INDOL-3-YL)-ETHYL]PYRROLIDINE; 1-[2-(1-PYRROLIDYL)ETHYL]INDOLE; "PYRROLIDYLTRYPTAMINE"

SYNTHESIS: To a well-stirred solution of 1.0 g indole in 15 mL TBME there was added, dropwise over the course of 20 min, a solution of 1.1 g oxalyl chloride in 15 mL TBME. Yellow crystals of indol-3-ylglyoxyl chloride appeared at about the half-addition point. Stirring was continued for an additional 10 min. This intermediate was removed by filtration, washed sparingly with TBME, and used directly in the following step. The above indol-3-ylglyoxyl chloride was added, a bit at a time, to 2.1 mL anhydrous pyrrolidine that was being vigorously stirred.



The color was discharged, and reaction mixture became almost colorless. To this there was added 80 mL of 1 N HCl, the mixture cooled, and the resulting solids removed by filtration, washed with H_2O and air-dried. This was recrystallized from 30 mL boiling CH_3CN (slow to dissolve and crystallize out) to give, after filtration, CH_3CN washing, and air drying, 0.87 g (42%) of indol-3-yl-N,N-tetramethyleneglyoxylamide with a mp of 219-220 °C. The literature reports a mp 224-225 °C. IR (in cm^{-1}): 753, 789, 834, 1143, 1161, 181, C=O 1615 (br), NH at 3150.

A solution of 0.76 g indol-3-yl-N,N-tetramethyleneglyoxylamide in 15 mL anhydrous dioxane was added, slowly, to 0.8 g LAH in 15 mL dioxane which was well-stirred and held at reflux temperature under an inert atmosphere. After the addition was complete, reflux was maintained for an additional 16 h, the reaction mixture cooled, and the excess hydride destroyed by the cautious addition of wet dioxane. The formed solids were removed by filtration, washed with hot dioxane, the filtrate and washings combined, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum. The residue was distilled at the KugelRohr at 0.05 mm/Hg, yielding a fraction boiling at 170-180 °C which spontaneously crystallized. Thus, there was obtained 0.35 g (52%) of N,N-tetramethylenetryptamine (pyr-T) with a mp 114-115. IR (cm^{-1}): 740, 784, 807, 886, 1011, 1108. MS (in m/z): $C_5H_{10}N^+$ 84 (100%); indolemethylene$^+$ 130 (7%); parent ion 214 (3%). A solution of this base in Et_2O treated with anhydrous HCl gave the hydrochloride salt which, on recrystallization from MeOH/benzene, had a mp 193-194 °C.

DOSAGE: unknown

DURATION: unknown

QUALITATIVE COMMENTS: (with 25 mg, orally) "There was a general malaise

without any particular spiritual or noble side to it. I was sick."

(with 50 mg, orally) "There is maybe something here, but it is unpleasant. Salivation, muscle and joint pains. I tried smoking it earlier and it was almost inactive. Certainly less potent than DMT or DET."

(with 70 mg, smoked) "This smells like a mixture of DMT and naphthalene. The effects began very soon, and led to an intense, but a little bit uncomfortable, high. I was distinctly dizzy, and the visuals were minor. I would classify this compound in the 'not too pleasant' category, certainly not colorful."

EXTENSIONS AND COMMENTARY: First of all, the name pyr-T, which is an abbreviation for "pyrrolidinyltryptamine," is out-and-out wrong. There is just one single nitrogen at the end of the tryptamine chain and it cannot be claimed by both halves of the name. It is intrinsic to the name pyrrolidine as well as to the name tryptamine. This is why the name is in quotation marks. This drug has occasionally been called PT in the popular literature, but choosing to spell it out as pyr-T allows a parallel code to be used with the piperidine and morpholine analogues. These two analogues are both described in the literature. The piperidine material (pip-T) is made via the glyoxylamide (mp 182-183 °C) which is reduced with LAH to the target amine (mp 149-150 °C, HCl salt 220-221 °C). The morpholine analogue (mor-T) also came to be via the glyoxylamide (mp 187-188 °C) and the reduction to the amine which can be an oil, but which has been reported to have a mp 145-147 °C. The only trials I know of with either of these is with mor-T which, as the fumarate salt, had no effects at all upon the i.m. injection of a 30 milligram bolus.

Actually, this neat trilogy of heterocyclics, the pyrrolidine ring, the piperidine ring, and the morpholine ring, have been the chemist's favorite for many years. Leaf through the "Known Tryptamines" appendix, and see how often you see stretched between the nitrogen substituents the phrases:

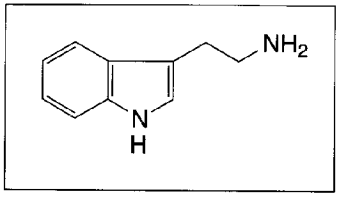
— CCCC —
— CCCCC —
— CCOCC —

These are the exact rings. They are easy to make; they add a sense of sophistication to an otherwise pedestrian scientific paper; and they often represent the inactive extremes in a receptor-site study of structure activity relationships of CNS-active agents. But the compounds represented here appear to have simply the wrong properties, somehow, and should not really be seriously considered in the quest for understanding of the remarkable actions of most of the psychedelic phenethylamines and tryptamines.

And yet no observation, favorable or unfavorable, deserves to be discarded. The very failure to act in an expected way might, if completely understood, add to our intimate understanding of the mystery of why these materials do what they do.

#53. T; TRYPTAMINE; INDOLE, 3-(2-AMINOETHYL); 3-(2-AMINOETHYL)INDOLE

SYNTHESIS: (from indole) To a cold solution of approximately 25% aqueous dimethylamine (most easily made by dissolving 20 g dimethylamine hydrochloride in 20 g cold 50% NaOH) there was added 30 mL acetic acid followed by 17.2 g 37% HCHO. This mixture was added to 23.4 g indole crystals, and the combination was allowed to stir overnight. This reaction was then quenched by pouring into 40 g KOH in 300 mL H_2O. A yellowish gum settled out, slowly solidified, and was washed with 2x100 mL H_2O. The yellow solids were dissolved in 100 mL CH_2Cl_2 and extracted with 2x200 mL 1 N H_2SO_4, the extracts pooled, and washed with an additional 50 mL CH_2Cl_2. The nearly colorless, aqueous phase was made basic with 25% NaOH, and extracted with 3x75 mL CH_2Cl_2. Removal of the solvent under vacuum yielded a white, solid residue which, on recrystallization from acetone, yielded 11.0 g 3-(dimethylaminomethyl)indole (gramine) as a loose white crystalline product with a mp 131-132 °C. IR (in cm^{-1}): 749, 832, 868, 1000, 1040, 1119 and 1174. MS (in m/z): indolemethylene$^+$ 130 (100%); parent ion 174 (21%). The yield is very dependent on the amount of H_2O present and the temperature of the reaction. Here, with H_2O intentionally introduced as a simplification, there was the generation of some 1,3-bis-(dimethylaminomethyl)indole (MS (in m/z): $C_3H_8N^+$ 58 (100%); indolemethylene$^+$ 129 (7%); parent ion 231 (3%)), considerable yellow gum not soluble in either CH_2Cl_2 or H_2O, and considerable recoverable indole. This yield (here, 32%) has been reported to approach quantitative with the use of anhydrous dimethylamine and only acetic acid as a solvent. To a solution of 15 g NaCN in 30 mL H_2O there was added a solution of 10.0 g 3-(dimethylaminomethyl)indole in 100 mL EtOH, and the reaction held at reflux for 80 h. The solvent was removed under vacuum and the semi-solid residue dissolved in CH_2Cl_2 and washed several times with dilute HCl (caution, HCN evolved). After removal of the solvent, the residue was distilled at the KugelRohr to give 7.1 g (yield of 79%) of indole-3-acetonitrile (bp 140-150 °C at 0.1 mm/Hg) as a white oil. IR (in cm^{-1}): 751, 824, 930, 1017, 1070, 1103; CN at 2265, NH at 3420. MS (in m/z): parent ions 155, 156 (100%, 66%); indolemethylene$^+$ 130 (56%). The product is a crystalline solid (mp 35-37 °C) but was used in the following reaction without further purification. From the distillation pot, the by-product indole-3-acetamide could be obtained, with a mp 150-151 °C from aqueous EtOH.



A solution of 6.0 g indole-3-acetonitrile in 15 mL anhydrous THF was added, dropwise, to 160 mL of a 1 M solution of LAH in THF, stirred and held under reflux conditions. After an additional 8 h reflux, the reaction was cooled, and the excess hydride and reaction complex were decomposed by the careful addition of

wet THF until the evolution of hydrogen ceased, then 25 mL 5% aqueous NaOH was added, followed by sufficient H_2O to leave the inorganic solids with a filterable texture (about 15 mL additional). These solids were removed by filtration, the filter cake washed with THF, the filtrate and washings combined, and the solvent removed under vacuum. The solid residue was recrystallized from CH_3CN to provide 5.3 g (86%) tryptamine as a cream colored crystal with a mp 112-114 °C. IR (in cm^{-1}): 751, 811, 882, 941, 1014, 1112 and 1128.

This synthetic scheme is probably not needed by the chemist. There are many commercial sources of indole and, for that matter, for gramine, for indoleacetonitrile, and for tryptamine itself. In general, the commercial price goes up modestly with each material named in this reaction scheme. Tryptamine itself, as the hydrochloride salt, is disproportionately expensive and, in most reactions, must be converted back to the free base before use.

DOSAGE: 250 mg, intravenously

DURATION: Very short

COMMENTS: (with up to 10 mg, intravenously) "There were no changes in blood pressure or self-rating scores."

(with 250 mg, intravenously) "Tryptamine was infused intravenously over a period of up to 7.5 minutes. Physical changes included an increase in blood pressure, in the amplitude of the patellar reflex, and in pupillary diameter. The subjective changes are not unlike those seen with small doses of LSD. A point-by-point comparison between the tryptamine and LSD syndromes reveals a close similarity which is consistent with the hypothesis that tryptamine and LSD have a common mode of action."

EXTENSION AND COMMENTARY: This quotation is from a paper by Martin and Sloan, published almost thirty years ago, that stands as our only measure of the human response to tryptamine. The first of the two reports in the comments took place 5 years earlier, with depressed patients and at very low levels of drug administration. It had already been established in rat and dog studies that tryptamine was known to enter the brain but, due to rapid metabolism, had only a short duration of central activity. Hence, the researchers in both these studies chose to employ an intravenous route of administration. There are a number of valuable points to be made in this latter report describing the 250 mg. study.

Clearly, the model drug in vogue at that time for central action was LSD, and all researchers felt that comparisons should be made to it, as sort of a gold standard. It was acknowledged that the setting in which an experiment took place could influence the outcome. Many studies with LSD were conducted in an environment that was quite different (in private living rooms, with good music and friendly faces) than these tryptamine experiments conducted in a clinical ward of

the Lexington Addiction Center, with automatic patellar reflex hammer strokes and polygraphic pupillary diameter measurements, conducted in what was in fact a narcotics prison.

Most instructive was the statement that the tryptamine syndrome was similar to the LSD syndrome. This equation has been broadly quoted, but it is valuable to read, first hand, the explicit observations of central activity that supported this conclusion. These are quoted here:

"Shortly after the onset of the infusions, three of the patients became aware of the experimental setting and complained of a heaviness, tiredness or numbness of the limbs which subsequently became generalized to other parts of the body. With continued infusion, a variety of other visceral symptoms and signs emerged which have been previously described following administration of LSD and mescaline, including nausea, vomiting, dizziness, sweating, acute or dulled hearing, metallic taste, and a heaviness of body. Further, in 2 of the 4 subjects, there were visual changes (subsequently described as a heaviness behind the eyes, a clouding of vision, and lines or cobwebs)."

The tryptamine experience sounds pretty heavy, and it is almost as if every negative LSD or mescaline property was exhumed and displayed, to justify tryptamine as being similar to this widely accepted psychedelic drug.

Why is tryptamine of any interest at all? Just as the simple compound phenethylamine was the nucleus for all of the potential psychedelic compounds in *PIHKAL*, so tryptamine plays a similar role as the nucleus of all drugs discussed in this volume. These are the structural basic-skeleton archetypes of these two corresponding classes of psychedelic drugs. Both are widely scattered throughout the plant kingdom, and they are both normal components of the human animal. They both have amino acid origins, phenylalanine for phenethylamine and tryptophan for tryptamine, and these amino acids are extremely important factors in human biochemistry. And they, each in turn, can only provoke pharmacological effects when administered parenterally at very high levels.

Tryptophan, the metabolic precursor to tryptamine, is itself a centrally active amino acid. There is a complex and little appreciated story associated with it as to its human psychopharmacology. Although tryptamine is only active parenterally, tryptophan is active orally and is directly converted to tryptamine, the two compounds must be considered in concert. What is the action of tryptophan, taken orally? Here are some quotations from the published literature, mostly with the voice of the giver, not the taker, with some copy taken from health-food store fliers of a decade ago.

COMMENTS: (with 2 g, orally) "I administered two grams to 7 normal subjects, and 5 of them became drowsy after 1-2 hours."

(with 2 g, orally) "The amino acid tryptophan is a safe, non-addictive sleeping aid which works because it is made into serotonin in the brain. Serotonin is the neurotransmitter which initiates sleep. Tryptophan is found in milk and

bananas and can sometimes be purchased in pill form. Two grams of tryptophan just before bed is very helpful in getting to sleep. For best results take it on an empty stomach. Although milk contains tryptophan, the pure amino acid is more effective."

(with 5 g, orally) "I took five grams orally several times over a period of days (to study urinary metabolites) and I did not expect any psychological effects. Within an hour, there was a slight dizziness, a feeling of light-headedness and some euphoria which was comparable to whiskey."

(with 6 g, orally) "We gave six grams tryptophan orally to seven subjects. All became listless and yawned frequently, and five of them slept between the periods of testing. Three were unable to remain awake for more than a few minutes. All were easily aroused however, and then felt euphoric and were unusually voluble and overactive. One showed marked social disinhibition in his behavior. Two were clumsy in turning and tandem walking. One had a frontal headache and another was dizzy without vertigo."

(with 10 g, orally) "We gave our sixteen normal subjects 10 g d,L-tryptophan orally. All experienced symptoms such as changes in perception (lightheadedness and dizziness) and changes in mood, mainly euphoria. None of the thirty-four chronic alcoholic subjects noted any symptoms at this dosage level."

(with 15 g, orally, with 150 mg iproniazid) "This was a daily treatment given to schizophrenic patients, tryptophan along with an antidepressant which is a monoamine oxidase inhibitor. Most showed marked changes such as an elevation in mood, an increased involvement with other people in their ward, and an increased extrovertism. A separate study of this combination with the addition of the amino acid L-methionine produced in about half of these patients a toxic or delirioid state."

CONTINUING COMMENTARY: Look at this fabulous story that unfolded some twenty years ago. It is completely coherent, and it is totally exciting. Let me try to distill the human information given above into a logical flow. Tryptophan, a natural and nutritionally essential amino-acid, is a centrally active intoxicant and sleep-provider in man. It is converted metabolically to tryptamine, which is a little bit psychedelic. When administered with methionine (another amino-acid known to methylate things) it produces methylated tryptamines, the two best-studied being N-methyltryptamine (NMT) and N,N-dimethyltryptamine (DMT). The effects that result are hard to categorize, reflecting the diagnostic status of the patient. But something happens. In short, tryptophan, alone or in combination with MAO inhibitors or methyl donors, is a fabulous tool for exploring brain function. And it was an easily available research tool, openly explored by many private individuals. It was inspiring a broad curiosity as to meeting a large number of human inadequacies.

Then, an incident occurred in 1989, at the Showa Denko company in Japan, where a change in the manufacturing procedure produced an impure product. The impurity led directly to a health problem, a condition with a flu-like syndrome called

Eosinophilia-Myalgia Syndrome (EMS), which caused some 1500 incidents in the United States, including 38 deaths. The FDA quite rightly removed tryptophan from the market on the 17th of November, 1989, and banned its distribution. The source of the health problem was quite quickly identified, and the production operation was changed back to the original process, and the tryptophan product was again available free of any toxic impurity. This freedom from any impurity was acknowledged by the FDA, but they transferred the toxic aspect of the substance from the impurity contained within it (now no longer present) to the substance itself. The implied declaration was that tryptophan was intrinsically toxic.

The sale of tryptophan as dietary supplements for man is now illegal. Dietary supplements to animal stock feed is okay. Tryptophan is available to hospitals for use in critical situations. Tryptophan is available as a prescription drug. But it is not available in the health food stores and so cannot be explored by the lay researcher. The world of inquiring into the action on normals, schizophrenics, alcoholics, people who are overweight, people who are depressed, is denied both to the private individual and to the clinical researcher. There are commercially available drugs, all approved, that can play the same role. Within four days of the announced ban of tryptophan (after the problem had been resolved and corrected) a broad promotion of Prozac (an antidepressant similar in action to Tryptophan) appeared in Newsweek (March 26, 1990). Prozac is still widely promoted. Tryptophan is still not available to the private individual. Both can play the role of being an effective sedative.

A quotation from the FDA "Dietary Supplement Task Force Report," page 2, June 15, 1993, deserves careful reading.

> "The [FDA] Task Force considered various issues in its deliberations, including ... what steps are necessary to ensure that the existence of dietary supplements on the market does not act as a disincentive for drug development."

What are dietary supplements? How might they get in the way of pharmaceutical industry creations? Where is the line to be drawn between nature and big business? What plants are there that might serve as health adjuncts? I truly think that we are being had by the powers that be, who are authorized to control our access to medicines. Today we cannot eat ABC because it contains an outlawed drug. Tomorrow we cannot eat DEF because it is suspected of containing an outlawed drug. The day after tomorrow, we cannot eat GHI because it has not been shown to be free of outlawed drugs. And yet, everything in the drug store had its origins somewhere in a botanist's observation or in a chemist's mistake. Where does this oppression stop? When do we say, hold, enough?

We must be free to eat this plant, and smell that flower, as we choose to. To deny us this right is to deny us a simple and basic freedom that is our Constitutional heritage. If I want to continue to eat bananas and drink milk, I will

do so, and get off my back. If I want to consume tryptophan because I feel it brings me closer to God and Jesus, or makes me sleep better, I will consume tryptophan. You, the empowered authority, will not tell me not to. As was so eloquently expressed in Leonard Bernstein's "West Side Story," when the group of heroes came up against the authorities, they said, "Hey, Officer Krupke, krup you!"

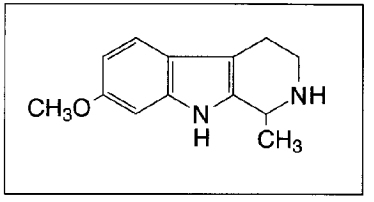
There are a pile of pharmacological details that should be collected and disposed of. For example, L-tryptophan is the natural and normal amino acid and yet it is more toxic than the unnatural d-isomer. The rat data would suggest that it might be a problem at something over a 100 gram dose, although I know no one who has nibbled that high. In fact, L-tryptophan is the most toxic of all the natural dietary amino acids (in rats at least). Interesting. But, so what? There is a botanical side to all of this. Gramine is a synthetic precursor of tryptamine, and yet it has been reported here and there as a natural plant component. The same is true for indole-3-ethanol. Yet, both of these can serve you in the laboratory for the synthesis of tryptamine and, of course, of DMT. The plant world seems to be fully aware of these same processes.

A final comment to connect man and plant. The primary animal metabolite of both tryptamine and of DMT is the corresponding indoleacetic acid which is itself a potent plant hormone. This just happens to be one of the most thoroughly studied plant growth hormones, and has been isolated from a number of natural sources. Less well studied is the reduction product of the intermediate aldehyde, by the action of monoamine oxidase, to the corresponding alcohol, indole-3-ethanol, or tryptophol. This rather rare plant stimulant has been found in cucumber seedlings, but has also been shown to be present in trace amounts (along with the hormone indoleacetic acid, MMT and DMT) in at least one Ayahuasca component, the Illinois Bundle-flower legume, *Desmanthus illinoensis*. Another circle has closed upon itself in an interesting way.

#54. TETRAHYDROHARMINE; HARMAN, 7-METHOXY-1,2,3,4-TETRAHYDRO; HARMINE, 1,2,3,4-TETRAHYDRO; β-CARBOLINE, 7-METHOXY-1-METHYL-1,2,3,4-TETRAHYDRO; 7-METHOXY-1,2,3,4-TETRAHYDROHARMAN; 1,2,3,4-TETRAHYDROHARMINE; 7-METHOXY-1-METHYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE; 7-MEO-THH; LEPTAFLORINE

SYNTHESIS: A stirred solution of 1.0 g harmaline hydrochloride in 25 mL H_2O was covered with a pad of Argon, and there was added 0.1 g PtO_2 followed by the dropwise addition of 0.4 g $NaBH_4$ in 4.0 mL H_2O over the course of 20 min. The pH was determined periodically and the reaction mixture was kept acidic during this

period by the addition of 1 N HCl as needed. The catalyst was removed by filtration through paper with H_2O washing, and the pale yellow filtrate made basic with the addition of aqueous NaOH. The cloudy basic suspension was extracted with 4x25 mL CH_2Cl_2, these extracts were pooled, and the solvent removed under vacuum. There was thus obtained 0.88 g of crude tetrahydroharmine as a white solid. A 0.25 g sample was recrystallized from MeOH to give a reference sample as white crystals with a mp 187-190 °C, IR (in cm^{-1}): 804, 902, 922, 943, 1036, 1157. MS (in m/z): 201 (100%); parent ion 216 (33%); 172 (20%). The remaining crude sample (0.60 g) was dissolved in 12 g IPA and treated with 8 drops of concentrated HCl (acidic to external pH paper) and allowed to stand for a day. There were deposited crystals which were removed by filtration, lightly washed with IPA, and dried at 100 °C to give tetrahydroharmine hydrochloride 0.53 g (75%) as a fine solid, with a greenish tinge, mp 232-234 °C. IR (in cm^{-1}): 789, 804, 816, 838, 1033, 1160.



DOSAGE: 300 mg, orally

DURATION: unknown

QUALITATIVE COMMENTS: (with 300 mg, orally) "At this dosage level there were subjective effects similar to what I had experienced with 100 milligrams of harmaline."

EXTENSIONS AND COMMENTARY: This one comment is the sum total of what I can find in the literature concerning the human activity of tetrahydroharmine. It was a study done with the synthetic racemate, whereas the natural isolate is the dextrorotatory isomer. It was a single trial. It was carried out in a single volunteer. There is no information given as to what this person's response had been to 100 milligrams harmaline. Tetrahydroharmine could very well be an extremely important factor in the study of plants known to promote materials such as DMT to oral activity. It is present (along with harmaline and harmine) in *Peganum harmala*, and has been reported as being present in levels equal to those of harmine in the analyses of ayahuasca samples (where harmaline itself is usually present in rather small amounts). And it is an effective monoamineoxidase inhibitor. The material is easily synthesized and it should not be difficult to resolve it into its optically opposite forms. Clinical studies would be extremely informative. In balance, the psychopharmacological activity of this plant isolate must be accepted as being essentially unknown.

The first isolation of tetrahydroharmine from the botanical world has an

interesting story attached to it. The major alkaloid known to be in *Banisteriopsis caapi* (back in 1920's when the Genus was still called *Banisteria*) was harmine. Some reports a few years later reported the presence of harmaline, but it was not until the 1950's that a careful chromatographic analysis of the plant revealed a third alkaloid. The apparent optical activity was discounted, and the isolated material was thought to be 6-methoxy-N,N-dimethyltryptamine (6-MeO-DMT). This was synthesized, and it wasn't quite right. In chemistry, not quite right means out and out wrong. Then the racemic (optically inactive) form of tetrahydroharmine was synthesized and not only was it spectroscopically identical to the dextrorotatory plant isolate ($[\alpha]_D$ +32°) but it had an identical infra-red spectrum, an identical melting point, and no depression with a mixed melting point. There are precious few optical isomers and racemates that can make that claim.

There are a number of other plants that are known to contain tetrahydroharmine and to have been used in various native preparations. I have recently learned of analysis of an Ayahuasca brew that had used the plant *Calliandra pentandra* as a component, instead of the usual *Psychotria viridis*. Ott's magnificent compendium *Pharmacotheon* makes mention of a *Calliandra augustifolia* as a component of ayahuasca, but there is no mention of this *pentandra* species. The preliminary analysis that I have been given of this decoction is that a component that had initially appeared to be DMT by HPLC analysis had proven to be tetrahydroharmine when assayed by GCMS. There was no detectable DMT present. And yet the material appears to have psychopharmacological activity.

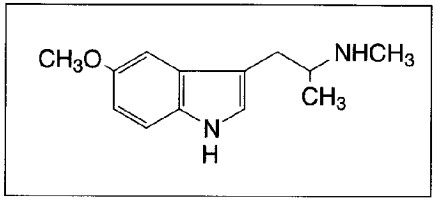
More studies on tetrahydroharmine are absolutely imperative.

#55. α,N,O-TMS; TRYPTAMINE, 5-METHOXY-α,N-DIMETHYL; INDOLE, 5-METHOXY-3-[2-(METHYLAMINO)PROPYL]; 5-METHOXY-α,N-DIMETHYLTRYPTAMINE; 5-METHOXY-3-[2-(METHYLAMINO)-PROPYL]INDOLE; α,N,O-TRIMETHYLSEROTONIN; SEROTONIN, α,N,O-TRIMETHYL

SYNTHESIS: To a solution of 1.21 g 5-methoxyindole-3-carboxaldehyde in 15 mL nitroethane there was added 0.3 g anhydrous ammonium acetate, and the mixture was held at steam-bath temperature. Periodic assay by TLC showed the reaction to be complete in 1.5 h. The volatiles were removed under vacuum, and the residue (1.58 g of rusty red crystals) was recrystallized from 15 mL boiling IPA. After filtration and air-drying, there was obtained 1.24 g (82%) of 5-methoxy-3-(2-nitropropenyl)indole as dull gold crystals with a melting point of 178-179 °C. The literature value is 182-184 °C.

A suspension of 1.7 g electrolytic iron dust in 10 mL of 80% aqueous acetic acid was heated on the steam bath until there were clear signs of hydrogen evolution.

To this stirred suspension there was added 0.50 g 5-methoxy-3-(2-nitropropenyl)indole a bit at a time, over the course of 2 min. The heating and stirring was continued for 30 min, by which time TLC analysis (CH_2Cl_2/hexane, silica) showed the starting material to be gone, and there were two new spots, one slower moving and one at the origin. The reaction mixture was poured into 100 mL of a H_2O/CH_2Cl_2 mixture, and filtered through paper. The two phases were separated, and the aqueous phases extracted with an additional 2x50 mL CH_2Cl_2. The pooled organic extracts were washed once with saturated aqueous K_2CO_3, and the solvent removed under vacuum. The resulting residue was distilled at 0.08 mm/Hg to give 5-methoxyindol-3-yl acetone as a colorless oil which came over at 215-230 °C. The product weighed 0.24 g, had a carbonyl absorption at 1710 cm^{-1}, and had an acceptable fragmentation pattern by GCMS.



To 20 mL methanol, there was added 1.17 g of 5-methoxyindol-3-yl acetone, 4.3 g CH_3NH_2 hydrochloride, 0.5 g $NaCNBH_3$ and sufficient concentrated HCl/MeOH to bring the pH down to a yellow color on damp, broad range pH paper. The reaction was stirred at room temperature, with periodic addition of more acid as needed, over the course of several days. The reaction mixture was poured into dilute sulfuric acid, washed twice with CH_2Cl_2, made basic with dilute NaOH, and extracted with 3x50 mL CH_2Cl_2. After the removal of the solvent under vacuum, the residue (0.76 g) was distilled at 180-190 °C at 0.05 mm/Hg to give 0.65 g α,N,O-trimethylserotonin (α,N,O-TMS) as a colorless oil. It did not crystallize, nor were any solid salts of it obtained. MS (in m/z): $C_3H_8N^+$ 58 (100%); indolemethylene$^+$ 161/160 (19, 7%); parent ion 218 (<1%).

DOSAGE: 10 - 20 mg, orally

DURATION: 6 - 8 h

QUALITATIVE COMMENTS: (with 16 mg, orally) "It was maybe a plus two, but there wasn't really much of anything. My body felt safe, was safe. The only strong negative, negative only to me, was the nature of my dreaming that night; shallow, a faint metallic flavor, a distinct lack of depth or dimension. A waste of good dreaming time."

(with 16 mg, orally) "I got as far as this would go, at about an hour and a quarter. There was nothing in the visual field, but I was unquestionably somewhere. I was quite horny, and the erotic was both excellent and satisfying. Tried writing, and it seemed easy. There was no fantasy, no color enhancement, and not much in the way of eye-dilation or appetite loss. Nothing much anywhere at all. As with Oakland, no there, there. And by the seventh hour, there was baseline, with a

residual feeling of having been cleansed."

(with 20 mg, orally) "I was in quite a depressed state, but I don't think it was the α,N,O-TMS. But it certainly didn't lift the depression. Everything I saw confirmed my growing despair about the human race and I concluded, after a few hours, that we have doomed ourselves. I am tired at being angry at it all. Enough already."

EXTENSIONS AND COMMENTARY: There is a sadness felt with most of the published efforts to form sweeping correlations between the structure of a molecule and its biological activity. This relationship is called a SAR, or a Structure Activity Relationship, and there are journals that are dedicated to just this form of analysis.

One needs a large collection of compounds of known structure, and all of them must be of known pharmacological activity. And one needs a computer of some sort. One considers all aspects of the structure such as bond energies, electronic charge densities, molecular lengths, widths and thicknesses, degrees of freedom or of constraint, anything that can be calculated or measured. Then one assigns an independent variable coefficient to everything, constructs some additive equation where these coefficients equal something else, and then compares that something else to the biological activity. Push the "go" button on the computer, and let everything be varied clear across the map, until the calculated solution of the equation makes the best match with the value of pharmacological activity. Then one has a SAR with a statistical measure of goodness of fit, and it then can be used to predict the activity of new structures, which are yet untried, pharmacologically.

And there is the essence of why this entire process is ineffective. Prediction is the heart of this procedure, and prediction is never brought to bear. Let us take a new structure that is not in the original collection of structures, and let us make a prediction as to its, let us say, psychedelic potency. But no one ever tries it out for any of a number of reasons. Maybe the new compound is never synthesized. Or maybe it is synthesized, but never evaluated pharmacologically. The synthesist does not care, or is uninterested, or is restrained by the legal complications that might ensue. Or he does explore it, but chooses not to publish. Almost never is a prediction tested. What is more likely to happen is that a new input of biological activity and structure variation is uncovered (for which there is no published prediction) and this data is tossed into the mill, and a new set of "more valid" coefficients is calculated, and the SAR becomes touted as a more accurate predictor. But, always remember that without prediction and challenge, there is no inventive value from the SAR game. It simply organizes what is known, but creates nothing new.

This is a role that I would have loved to see α,N,O-TMS play. At the time of its first synthesis its biological activity was, by definition, completely unknown. Let's cast its shadow up against the structures that were known, and with known activity. What would you predict? The most logical archetype to use as a starting point is the primary amine homologue, α,O-DMS. This is an extremely potent, quite long-lived tryptamine that still ranks up there as the most potent, or nearly so, of all the simple substituted tryptamines. It is orally active. It lasts for many hours. It is completely wild as to visual distortions and illusions. It consistently leads to dramatic, perhaps frightening, but certainly memorable dreams. Three or four milligrams are unmistakably adequate. I would have loved to have had an SAR jock predict what changes would come from the simple addition of an N-methyl group. No one out there predicted this for me, and I have now completely abandoned the art of prediction, at least via the SAR technique. My motto is, make 'em and taste 'em.

To base structures that are stimulants (amphetamine, for example) an added N-methyl group enhances potency and richness. With MDA, for example, one gets MDMA, not more potent, but of an entirely different form of psychological magic. However, with all the other explored primary amine phenethylamine psychedelics, the potency and the quality of action are effectively lost. With tryptamines, however, the N-methyl groups appear to be needed for full, robust activity. Here, the loss of an N-methyl group might well detract from full potency, and the final unmethylated product (DMT becoming simply tryptamine) will be relatively weak and uninteresting. If α,N,O-TMS had been active at one milligram, then the MDMA explanation is obviously correct. If α,N,O-TMS had been active only at a meager level of twenty milligrams, then the DMT explanation would appear to be correct. It is much less active. It is not spectacular. All you SAR scientists, take this new data, toss it into the maws of computer calculation, and come out with better coefficients.

With this, now, as a challenge, predict for me the potency of α,N,N,O-tetramethylserotonin. Here is a compound that has not, to my knowledge, been synthesized. It carries the second N-methyl group (closer to DMT at the nitrogen atom, and probably more potent) and yet a structural kiss of death (as to potency) in the MDA/MDMA world. Will it be up? Will it be down? I am afraid that the "make 'em and taste 'em" procedure is the only one that I can trust.

Good luck.